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THE RESULTS OF SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

CARL A. HEDBLOM[3]

Surgical treatment of pulmonary tuberculosis is generally considered to include all forms of mechanical collapse with the exception of that produced by pneumothorax therapy. It comprises extrapleural thoracoplasty, paralysis of the diaphragm, section of the scaleni muscles, pneumolysis with or without plombage, drainage of tuberculous cavities with secondary plastics, and various combinations of these methods including that with pneumothorax. Extrapleural pneumothorax, section of the intercostal nerves, ligation of the pulmonary artery, and sympathetic-nerve resection, may perhaps be dismissed, with passing mention, as still in the experimental stage. Drainage of chronic cavities and excision of their outer walls have a very limited indication.

None of the various surgical procedures can be said to be standardized with respect to their technical aspects. Total posterior extrapleural thoracoplasty (Sauerbruch or Brauer), as performed in different clinics, varies considerably as to length of ribs resected. Most thoracic surgeons perform it in two stages, some in one and some in three. Some begin from below, others from above. In recent years, partial posterior thoracoplasty involving resection of relatively long segments of 7 ribs only, or subtotal resection of the upper three, four or five is finding increasing favor for certain indications. Supplementary resection of the anterolateral segments is performed to increase the collapse of both the total and partial posterior resection.

Phrenic-nerve crushing or resection, though most often used in combination with other methods, is generally recognized as having definite indications as an independent procedure and, as to technical details, is then perhaps the most standardized of all methods.

[1] From the Department of Surgery, College of Medicine, University of Illinois, Chicago, Illinois.

[2] Read at a joint session of the Clinical and Pathological Sections at the thirtieth meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 17, 1934.

[3] This paper was received and accepted for publication shortly before Doctor Hedblom's death, and is therefore being published without the benefit of his corrections or revisions.

Apical pneumolysis with plombage varies greatly in practice as to choice of material, size of the plombage mass, and as to approach.

The combined procedures for unilateral collapse include total or partial pneumothorax, phrenic-nerve resection with division of the scaleni and with pneumolysis, and plombage as an auxillary to partial or total thoracoplasty. In bilateral tuberculosis, pneumothorax has been used on one side and a phrenic resection, plombage or thoracoplasty on the other, or bilateral phrenicoexairesis.

The indications for the different procedures also vary greatly. The type of the pathological process, whether predominantly exudative or proliferative, the size and location of a cavity, the degree of individual resistance, the extent and duration of the process, the age, sex and constitutional make-up of the patient, complications such as extrapulmonary tuberculosis, tuberculous empyema and visceral damage,—all influence the results of treatment. In case of bilateral involvement, evident clinically, the degree of activity and extent of even a healed lesion are of prime importance.

In evaluating results the time element is also an important factor. A patient may be greatly improved or symptom-free for months and even years after treatment, and yet eventually perish from the disease because of failure of the surgical treatment of a given lesion, or in spite of its successful treatment. The relief of symptoms, prolongation of life and degree of rehabilitation also enter into evaluation of results.

Such a diversity of variable factors in considerable measure vitiate the significance of comparative statistics, and yet, as in any other field of clinical medicine, they furnish the only means of arriving at a perspective of what has been accomplished, and of plotting the course of future trends. As actual figures are absolutely necessary for estimating results, and so for fulfillment of the assignment given me in this symposium, no apologies are offered for the statistical presentation which follows.

This study is based on a review of the author's experience with 200 thoracoplasty cases, and on 4,535 from the literature. A brief survey is added of the more recent results of partial thoracoplasty, of phrenicoexairesis as an independent procedure, and of pneumolysis with plombage.

The age and sex of the patients in the author's thoracoplasty series are given in table 1.

TABLE 1

Ages of patients

	MALE	FEMALE	TOTAL
years			
15–19	1	3	4
20–29	36	44	80
30–39	50	36	86
40–49	16	11	27
50–59	3	0	3
Totals	106	94	200

It will be noted that 4 were under 20 years of age, 30 were above 40 years, and of this group 12 were above 45. The sex distribution was almost equal.

The side involved is given in table 2.

TABLE 2

Sex and side involved

	CASES WITHOUT EMPYEMA	CASES WITH EMPYEMA	TOTAL
Male: right side	38	9	47
Male: left side	50	9	59
Female: right side	27	3	30
Female: left side	49	15	64
Male and female: right side	65	11	76
Male and female: left side	99	25	124
Totals	164	36	200

The empyema in 22 cases was a complication of pneumothorax treatment. Twenty-four were secondarily infected. It will be noted that a little more than 60 per cent were on the left side.

The duration of the disease from the time pulmonary tuberculosis was definitely diagnosed is shown in table 3.

TABLE 3

Duration of pulmonary tuberculosis

	MALE	FEMALE	TOTAL
mos. mos.			
6	1		1
7–12	5	2	7
yrs.			
13– 2	22	26	48
25– 3	14	13	27
37– 4	11	13	24
49– 5	8	13	21
61– 6	6	6	12
73– 7	11	4	15
85– 8	8	5	13
97– 9	2	3	5
109–10	4	3	7
yrs.			
10–15	11	3	14
15–20	2	2	4
20–25	1	0	1
25–30	0	1	1
Totals.....	106	94	200

The disease is often present for months or even years before being recognized. It follows therefore that the duration in general is longer than as given. As will be noted, it had been given as of less than one year's duration in 8 (3.4 per cent), but in most of these there was evidence that it had been present considerably longer. In a little over a third of the cases the duration was over 5 years, and in about 10 per cent over 10 years. The average age for males was greater than for females.

The results are presented as to operative complications, early and late mortality, with causes of death and as to degree of improvement and duration of favorable outcome. Since there is no standard classification of results an arbitrary one must be chosen. Sauerbruch's classification is into (1) early deaths: (a) during the first week, (b) during the 2nd to 8th weeks; and (2) late deaths: (a) during the 1st year, (b) during the 2nd year; (3) unimproved; (4) unchanged; (5) improved; (6) markedly improved; (7) cured (*Heilung.*) As "greatly improved" Sauerbruch includes those who are fever-free, raise a few cubic centimetres of bacilli-free sputum and who can do some work; as "cured", those fever- and bacilli-free for more than $1\frac{1}{2}$ years after operation, and who

are able to work. Since ability to work varies so greatly with sex and occupation, and since a few cubic centimetres of bacilli-free sputum may well come from a persistent bronchitis, the distinction between the last two groups seems almost too finely drawn.

Bull classifies results as follows: postoperative deaths as those occurring within the first 8 weeks and those later; the others into five groups: group 1, able to work, without bacilli, and symptom-free; group 2, able to do some work, not entirely symptom-free, and bacilli may be present in the sputum; group 3, not able to work, not bacilli-free; group 4, results not yet evident; and group 5, not traced.

At the last International Tuberculosis Congress, Bull reported a series of 401 personal and collected cases, so classified and studied in detail with special reference to times and causes of deaths, and as to the permanence of result. At the same Congress and later, others have similarly reported relatively large series. Because of the simplicity and practicability of the classification and the relatively large number of reported cases that lend themselves to such a subgrouping, it has been adopted for this study.

In this classification it will be noted that the cases group themselves into those living and those dead at the time of report, with a few additional untraced. Grouping deaths by time-intervals since operation avoids the difficulty of trying to reconcile conflicting opinions as to what constitute operative deaths. Those occurring within the first two weeks are probably almost exclusively due to the operation. A large number of these in the second month and some later are also attributable to it. Deaths during the first 8 weeks and not due to the operation as such may be due to an accident predisposed to by the operation, or to progress of the disease in a patient operated as a result of poor selection. The distinction between operative and nonoperative deaths in any case seems of secondary importance. However, in the tables the classifications used by the various authors are indicated wherever possible.

The mortality within 8 weeks is given in table 4.

TABLE 4

Mortality as reported within eight weeks after operation
Total and partial thoracoplasty

AUTHOR	YEAR	CASES	DEATHS	PER CENT
Hedblom	1934	164	17	10.3
Sauerbruch	1930	701	93	13.2
O'Brien	1934	388	22	5.6
Kinsella	1934	243	20	8.2
Thearle	1934	242	23	9.5
Schedtler	1931	200	17	8.5
Coryllos	1934	181	28	16.0
Denk and Domanig	1931	175	29	16.9
Bull	1930	168	15	8.9
Hegner	1934	168	21	12.5
Alexander	1934	162	25	15.4
Matson	1934	150	9	5.1
Key	1930	132	13	9.8
Bull (collected)	1930	129	21	16.3
Archibald	1930	117	9	7.7
Tandberg (Bull)	1930	104	8	7.8
Eloesser	1934	100	3	3.0
Huber and Waitz	1932	80	9	11.2
Jessen	1930	62	8	12.9
Davies	1930	46	5	10.8
Beye	1934	38	5	13.1
Dolley	1934	26	2	7.9
Decker	1930	19	4	21.0
Faltin	1928	15	4	21.0
Totals		3810	410	10.5

My own mortality in 164 cases exclusive of the cases with complicating empyema was 10.3 per cent.

The individual mortality varies between 3.0 per cent and 21.0 per cent. The combined mortality in 3,810 cases is 10.5 per cent.

Several authors reported their early mortality as after 2 to 12 weeks as shown in table 5.

TABLE 5

Mortality as reported 2 to 12 weeks after operation

Total and partial thoracoplasties

AUTHOR	YEAR	CASES	WEEKS	DEATHS	PER CENT
Gravesen	1930	211	6	16	7.6
Lambert and Berry	1930	100		25	25.0
Bruns and Casper	1930	92	12	21	22.8
Berard and Delgoffe	1927	91	2	17	18.6
Nystrom	1931	95	4	14	14.7
Carter	1931	53	12	4	7.5
Mauere and Rolland	1930	42	4	3	7.1
Eizaguierre	1930	41	12	4	9.9
Sachs	1930	36	2	7	19.4
Piotet and Eureh	1930	31	4	4	12.9
Totals		792		115	14.5

It will be noted that in some series the two-week mortality was greater than in others after 12 weeks. It must be emphasized that in view of the wide range of operative indications, and of type of individual with respect to social status, no conclusive significance can be attached to the figures in either table with respect to the operative procedure as such. They do represent the actual mortality following the operation within the time limits given.

Those surgeons who include a considerable proportion of only fair risks and such as may be considered as on the border-line of operability will have a higher mortality rate; but, other conditions being equal, they will have materially improved or cured a larger proportion of patients than those whose indications are more rigid and whose mortality rate is therefore lower. The average mortality for this series is 14.5 per cent. Combining tables 4 and 5 the average mortality within 12 weeks among 4,602 patients was 11.2 per cent.

Many surgeons report a lower postoperative mortality for their more recent series than in their earlier experience. Gravesen had 10 per cent mortality in his first 100 cases and 5.4 per cent in the next 111 cases. Others report a more considerable reduction but such later series include a large proportion of partial thoracoplasties.

Many authors have subdivided their cases into groups: favorable, mediocre, and unfavorable, as suggested by Archibald. As one would expect, they show a large proportion of very good results and a low

mortality for the favorable group and comparatively poor results and high mortality for the relatively unfavorable group of cases.

A few authors reporting large series of cases have given the mortality rates at intervals from a few weeks to years after operation as shown in table 6.

My own experience given in the first column of table 6 shows that about 43 per cent of all deaths occurred during the first 8 weeks. Sauerbruch's experience is about the same. For the whole group the mortality during the first 8 weeks represents from about one-fourth to nearly

TABLE 6

Death-rate of patients in relation to time-interval between operation and death

AUTHOR	HEDBLOM	SAUERBRUCH	BULL, ET. AL.	SCHEDTLER	KEY	DENK AND DOMANIG	NYSTROM	JESSEN	CARTER
Patients	161	701	401	200	190	109	95	61	52
Deaths within 7 days	2.4	3.2	5.5		1.1	14.67		4.9	3.8
Within 14 days	4.8		8.5		4.2	23.85		8.2	11.5
Within 21 days						26.6	14.7		
Within 28 days		13.2	9.5		7.4		14.7	9.8	
Within 42 days									
Within 2 months	10.5		11.0	8.5	9.5			11.5	
Within 3 months	10.5		13.5		10.5		22.1		
Within 6 months	11.8		15.75		11.1	37.6	23.1		
Within 12 months	14.9	22.2	18.0	20.0	17.4	46.8	26.3	11.5	17.0
Within 2 years	16.1		22.1	25.5	20.0	55.9	30.5	14.8	
Within 3 years	16.7		26.4	28.0	26.3	60.5	30.5		19.2
Within 4 years	18.0		30.9	31.0	26.8			16.4	21.1
Within 5 years	23.6		34.5	32.5			32.6		
Within 6 years	24.2		36.2	33.0					
Within 7 years									
Within 8 years							34.7		
Within 9 years				33.5	27.9	61.4			
Within 10 years									
Within 11 years		29.5			28.9				

one-half of the total. The later mortalities shown in this table are discussed under that heading.

The mortality during the first 8 weeks after operation with relation to sex and side operated upon is shown in table 7.

My own figures in the first section of table 7 show a higher mortality rate for males than for females, and for left-sided than for right-sided lesions; in the male the mortality is higher for left-sided lesions, and in the female for those on the right. Bull, in his own and collected series,

TABLE 7

Early mortality in relation to sex and side operated upon

	HEDBLOM			BULL			TANDBERG			BULL COLLECTED			KEY		
	Total number	Deaths	Rate	Total number	Deaths	Rate	Total number	Deaths	Rate	Total number	Deaths	Rate	Total number	Deaths	Rate
Male	88	10	11.7	77	8	10.4	46	7	15.2	62	9	14.5	34	3	9.0
Female	76	7	9.2	91	7	7.7	58	2	3.4	67	12	18.0	39	4	10.0
Right side	65	5	7.7	68	11	16.2	46	7	15.2	63	15	23.8	36	4	9.4
Left side	99	12	12.1	100	4	4.0	58	2	1.7	66	6	9.1	37	3	9.5
Male															
Right side	38	1	2.6	32	7	21.7	19	5	26.2	36	9	25.0	12	1	6.5
Left side	50	9	18.0	45	1	2.2	27	2	7.4	26	0	0.0	22	2	11.2
Female															
Right side	27	4	14.9	36	4	11.1	27	1	3.7	27	6	22.2	24	3	12.8
Left side	49	3	6.1	55	3	5.5	31	0	0.0	40	6	15.0	15	1	8.1
Totals	164	17		168	15		104	8		129	21		73	7	

	NYSTROM			JESSEN			DENK AND DOMANIG			CORYLLOS			COMBINED		
	Total number	Deaths	Rate	Total number	Deaths	Rate	Total number	Deaths	Rate	Total number	Deaths	Rate	Total number	Deaths	Rate
Male	45	9	20.0	30	1	3.3	100	18	18.0	64	16	25.0	543	81	14.8
Female	50	7	14.0	31	6	19.3	75	11	14.6	106	16	15.0	593	72	12.1
Right side	41	8	19.5	29	5	17.0	71	15	21.1	68	11	16.1	486	81	16.6
Left side	54	8	14.8	32	2	6.2	104	14	13.4	102	21	20.6	650	72	11.0
Male															
Right side	20	4	20.0	12	1	8.3	43	10	23.3	32	7	21.8	243	45	18.4
Left side	25	5	20.0	18	0	0.0	57	8	14.0	32	9	28.1	300	36	11.9
Female															
Right side	21	4	19.0	17	4	23.5	28	5	17.8	36	4	11.1	243	35	14.3
Left side	29	3	10.3	14	2	14.2	47	6	12.7	70	12	17.1	350	36	10.2
Totals	95	16		61	9		175	29		170	32		1,139	152	

including Tandberg's, on the contrary records a higher rate for males and a much higher rate for the right- than for the left-sided lesions, particularly in the male. Key's and Coryllos's figures correspond roughly with my own: those of Jessen and of Denk and Domanig (7) with those of Bull. It is quite clear from table 7 that the greatly increased hazard of operation for right-sided lesions, noted by Bull and his coworkers, is not a general experience. On the contrary, Key and Coryllos and my own mortalities for left-sided lesions, as stated, have been higher than for those on the right side. The combined experience in the 9 series, totalling 1,139 cases, does show a higher male and right-sided mortality, but this is because of the preponderance in numbers of the cases of the series grouped with those of Bull.

There must be some reason for this marked individual difference in results. If the high mortality in males following a one- or two-stage operation is due to the mechanical embarrassment of the venous return due to compression and distortion of the auricles and vena cava (Bull, Jessen, Hauke) or possibly due to disturbed cardiac innervation (Sauerbruch), it would be reasonable to expect a lower mortality from operations in three or more stages, as performed by the author, with a resulting much more gradual collapse, allowing time for circulatory readjustment. Bull's findings of 11.7 per cent mortality among 43 patients with right-sided lesions operated in two stages, and 37.5 per cent mortality among 40 operated in one stage, support this view.

Sauerbruch records late results in 54 cases of right-sided and 63 left-sided lesions, as follows: right side, 15 per cent early deaths; 22 per cent later deaths; 17 per cent unchanged; 13 per cent improved; 22 per cent bacilli-free and 11 per cent cured; and in the left-sided, 8 per cent early deaths; 6 per cent late deaths; 6 per cent unchanged; 30 per cent improved; 28 per cent bacilli-free and 22 per cent cured. My own results show as good later results for the right side as for the left.

The time of death and relation to operative stages in my series are shown in tables 8 and 9.

TABLE 8

Time of death: Hedblom's series

	UNCOMPLICATED	EMPYEMA CASES	TOTAL
1st week	4	4	8
8th–14th day	4	1	5
15th day–2nd month	9	3	12
2 months– 3 months			
3 months– 6 months	2	1	3
6 months–12 months	5	3	8
1 year–2 years	2	0	2
2 years–3 years	1	2	3
3 years–4 years	2	1	3
4 years–5 years	9	0	9
5 years–6 years	1	0	1
Totals	39	15	54

TABLE 9

Mortality in relation to stage of thoracoplasty: Hedblom's series

STAGE THORACOPLASTY	UNCOMPLICATED	EMPYEMA CASES	TOTAL
First	4	5	9
Second	5	0	5
Third completed	2	2	4
Third incompleted	1	0	1
Fourth completed	1	0	1
Secondary anterolateral, 1st stage	3	0	3
Secondary anterolateral, 2nd stage	0	1	1
Secondary anterolateral, 3rd stage	1	0	1
Totals	17	8	25

The causes of early death are given in table 10.

TABLE 10

Causes of death within eight weeks after operation

TIME	NUMBER	CAUSES OF DEATH
1st day	1	Fat embolism (empyema case)
2nd day	1	Respiratory failure
2nd day	1	Cardiac failure; old endocarditis
2nd day	1	Shock (empyema case)
3rd day	1	Cardiac failure
4th day	1	Tuberculous pneumonia, peritonitis and laryngitis
5th day	1	Suffocation from ruptured empyema into bronchus
6th day	1	Diffuse cellulitis from wound infection (empyema case)
2nd week	2	Cardiac failure
2nd week	1	Pneumonia opposite lung (empyema case)
2nd week	1	Tuberculous meningitis
2nd week	1	Mesenteric thrombosis
3rd week	1	Pulmonary embolism
3rd week	1	Septicaemia (streptococci in blood-culture)
3rd week	1	Spontaneous pneumothorax
3rd week	2	Cardiac failure
4th week	3	Extension of tuberculosis (two empyema cases)
4th week	1	Cardiac failure
5th–8th week	1	Bronchopneumonia
5th–8th week	2	Extension of tuberculosis (one empyema case)

Eight of the 25 cases were complicated by empyema. Five deaths followed completion of thoracoplasty and fifteen before it was completed, and five followed secondary anterolateral thoracoplasty.

As mentioned in table 8, eight of the 25 patients in my series had a complicating empyema at operation. Seven died of cardiac failure, two of wound infection, ten from pulmonary complications including one of respiratory failure the second day, two of embolism, one of spontaneous pneumothorax and one of rupture of a clinically unrecognized empyema into a bronchus following the second stage of a three-stage thoracoplasty.

Of the combined series, 18 (8.3 per cent) died of shock; 43 (18.7 per cent) from heart failure. If mediastinal flutter is added to this group the percentage reaches 22.1 per cent. Wound infection accounted for 18 (8.3 per cent). Several additional deaths from empyema were attributed to wound infection. Pneumonia, nonspecific and tuberculous,

and "extension of the infection," mostly pulmonary, include 78, or about 30.4 per cent.

TABLE 11

	WITHIN 8 WEEKS AFTER OPERATION			LATER THAN 8 WEEKS AFTER OPERATION		
	Author's	Collected	Combined	Author's	Collected	Combined
Shock	1	17	18			
Mediastinal flutter		8	8			
Haemorrhage		4	4			
Death on table		2	2			
Heart failure	7	36	43	2	1	3
Cerebral embolism		2	2			
Pulmonary embolism	2	4	6			
Pneumonia	2	23	25	4	1	5
Tuberculous pneumonia	1	6	7			
Miliary tuberculosis		7	7			
Respiratory failure	1		1			
Pulmonary oedema		2	2			
Meningitis	1	1	2			
Septicaemia	1	2	3	1		
Suffocation	1	1	2			
Massive collapse		4	4			
Wound infection	1	13	14		2	2
Gas-bacillus infection		1	1			
Toxic absorption		8	8			
Spinal anaesthesia		1	1			
Toxic goitre		1	1			
Mesenteric thrombosis	1		1			
Spontaneous pneumothorax	1	5	6			
Typhoid fever		1	1			
Empyema		8	8		2	2
Bilateral tuberculosis		2	2			
Extension tuberculosis	5	41	46	18	50	68
Brain tumor		1	1		2	2
Encephalitis		1	1			
Uraemia		1	1			
Diabetic coma		1	1			
Accidental deaths				2	1	3
Amyloidosis				2		2
Pericarditis		1	1			
Totals	25	205	230	29	61	89

Denk states that season plays an important rôle in mortality. He found that in 133 stages of operation performed between April and

September the postoperative mortality was 4.5 per cent; of 165 between October and May it was 13.8 per cent. My own figures for the winter season are 334 stages with a mortality of 2.1 per cent and for the summer 273 operations with a mortality of 6.2 per cent. The experiences of others as to seasonal mortality would be of interest.

The causes of the author's late deaths is shown in the left-hand columns in table 11.

It will be noted in table 11 that, in one-third of the cases in my series, death was due to causes independent of pulmonary tuberculosis. One of the patients with amyloidosis developed it very rapidly following a posterior thoracoplasty and never was in condition for a completion of the collapse. The other refused the operation for the residual empyema cavity and lived about 4 years after the posterior thoracoplasty. In the combined series 68 (76 per cent) were due to extension of the tuberculosis and this extension was mostly pulmonary.

The early and late death-rates in my own series and those of other writers who have recorded the time of death in some detail were given in table 6. The progressive mortality percentage in the several series is well shown in a graph that was constructed from this table but which is not shown here.

The number of patients in group 1 (living, symptom-free and able to work) is shown in table 12, with the number of years of freedom from symptoms since operation.

TABLE 12

Group 1: living and essentially symptom-free and able to work: no tubercle bacilli in sputum

Years after operations

AUTHOR	YEAR	CASES	1	2	3	4	5	6	7	8	9	10	11	12	13	14	TOTAL
Hedblom	1934	200	9	10	18	17	16	12	3	6							91
Bull, *et al*	1930	401	13	14	24	17	16	16	11	7	9	4	3	0	0	2	136
Key	1930	132	13	9	7	5	5	5	6	2	2	1	2	3	0	0	60
Schedtler	1931	200	19	19	14	13	7	7	4	1	0	2	0	0	0	1	87
Nystrom	1931	50	3	1	0	0	0	4	3	2	1	1	0	0	3	0	18
Denk and Domanig	1930	109	3	3	9	11	8	7	7	3	3	1	0	0	0	0	54
Berard and Delgoffe	1927	91	1	5	0	7	3	3	3	0	0	1	0	1	1	1	26
Carter	1931	52	0	0	3	5	4	2	8	2	0	0	0	0	0	0	24
Totals		1,235	61	61	75	75	59	56	45	23	15	10	5	4	4	4	496

Note: 87 per cent of the group, 2 years or more after operation; 45.1 per cent, more than 5 years after operation.

My own series shows in this group 45.5 per cent of all operated cases after 1 year, and 41 per cent after 2 years. Of a total of 1,235 patients, 496, or 40.1 per cent, were in this group after 1 year and 35.4 per cent more than 2 years.

The number in group 2 (living and able to do some work but not entirely bacilli- or symptom-free) is given in table 13, showing 182, or 14.7 per cent, were in this group after 1 year after operation, and 10.9 per cent after 2 years.

TABLE 13

Group 2: living and able to do some work: not symptom-free

Years after operations

AUTHOR	YEAR	CASES	1	2	3	4	5	6	7	8	9	10	11	12	13	14	TOTAL
Hedblom	1934	200	4	0	2	0	2	1	0	1	0	0	0	0	0	0	10
Bull, *et al*	1930	401	22	10	12	7	6	2	5	1	0	1	0	0	0	0	66
Key	1930	132	5	3	2	0	2	1	0	0	2	0	0	1	0	0	16
Schedtler	1931	200	7	12	2	6	8	0	2	0	0	0	0	0	0	0	37
Nystrom	1931	50	0	2	1	1	0	1	1	1	1	0	0	0	0	0	8
Denk and Domanig	1927	109	4	4	5	2	2	1	1	0	2	0	0	0	0	0	21
Berard and Delgoffe	1927	91	7	4	3	1	1	0	0	0	0	0	0	0	0	0	16
Carter	1931	52	0	0	1	2	3	1	1	0	0	0	0	0	0	0	8
Totals		1,235	49	35	28	19	24	7	10	3	5	1	0	1	0	0	182

Note: 73 per cent of the group 2 years or more after operation; 28 per cent of the group 5 years or more after operation.

The summary of the results in 8 series of cases totalling 1,239 cases is given in table 14.

TABLE 14

Summary of results one or more years after thoracoplasty

AUTHOR	CASES	LIVING					UNKNOWN	DEAD: TIME AFTER OPERATION											Total dead
		1	2	3	4	Total	5	1st 8 wks.	9 wks. to 6 mos.	6–12 mos.	years 2	3	4	5	6	7	8	9	11	
Hedblom	168	91	10	10		111	3	25	3	5	5	4	2	9	1	0	0	0	54
Bull, *et al*	381	136	66	21		223	6	43	19	9	17	17	18	15	6	3	3	2	0	152
Schedtler	200	87	39	3		129	4	17	0	23	11	5	6	3	1	0	0	1	0	67
Denk and Domanig	176	55	21	8		84	25	29	12	10	10	5	0	0	0	0	1	0	0	67
Key	132	60	16	6		82	4	13	3	8	5	9	3	1	0	0	0	2	2	46
Huber and Waitz	80	21	12	2		35	7	9	8	4	5	1	3	2	0	2	2	1	1	38
Carter	52	24	8	2	7	41	0	6	2	0	0	0	2	1	0	0	0	0	0	11
Nystrom	50	18	8	0		26	2	8	2	5	5	0	1	0	0	1	0	0	0	22
Totals	1,239	492	180	52	7	731	51	150	49	64	58	41	35	31	8	6	6	6	3	457

Of the total number, 731, or 59 per cent, were living; 457, or 38.9 per cent, dead; and 51, or 4.1 per cent, were untraced. Of the living, 67.3 per cent were in group 1; 24.6 per cent in group 2; 7.1 per cent in group 3; and 9 per cent in group 4. Of the 457 dead, 32.8 per cent of the total number died within the first 8 weeks after operation; 24.7 died within the 3rd to 12th months; 36.1 per cent during the next 4 years; and 6.3 per cent from the 6th to 11th years.

In table 15 is shown results similar to those in table 14, except for lack of details as to time of postoperative deaths in another combined group.

Among 2,523 cases, 1,653 (65.5 per cent) were living at the time of the reports; 83 (3.3 per cent) were untraced and 787 (31.2 per cent) were dead. Of the living, 50.8 per cent were in group 1, 39.6 per cent in group 2, and 9.5 per cent in group 3. The higher proportion of patients living in the series in table 15 is doubtless due to the fact that these patients had been followed a shorter period of time.

Combining the results of tables 14 and 15, as shown in table 16, we have 3,762 patients, showing 63.4 per cent living, 3.5 per cent untraced, and 33.0 per cent dead.

Of the total number operated upon, 35.4 per cent were clinically cured, and 22.1 per cent improved, making a total of 57.5 per cent relatively favorable results, during a period of observation of from 1 to 11 years. If the deaths from causes not connected with the operation or extension of the tuberculosis are subtracted the proportion of favorable results is very much greater.

For purposes of comparison the results of thoracoplasty in 1,159 cases collected from the literature and published in 1926 by Alexander, and those of Sauerbruch in 1930 among "about 1,200" from his own clinic, are of interest. Alexander found 36.8 per cent clinically cured; 24.2 per cent improved; 5.25 per cent unchanged or worse; and 33.5 per cent dead. Sauerbruch reports 40 per cent of clinical cures, and the combined early and late mortality 12 to 23 per cent.

Many important series of cases reported since 1926 have not been included in the compilation of tables because the material did not lend itself to the classification adopted. Among such series may be mentioned the following: Neumann, 100 cases with marked improvement in 40 per cent; Hauke, 200 cases of thoracoplasty, of which 40 per cent were clinically healed and able to work, 35 per cent improved, the "early" operative mortality 4–8 per cent; the later mortality "months to years,"

TABLE 15

Summary of results one or more years after operation

AUTHOR	CASES	LIVING				UNKNOWN 5	TIME OF DEATH AFTER OPERATION	TOTAL
		1	2	3	Total			
Sauerbruch	701	179	247	30	456	38	1st–4th wk. 93; to 2d yr. 63; later 51	207
Thearle	242	80	51	4	135	10	1st wk. 23; later 74	97
O'Brien	237	85	82	26	193		1st 8 wk. 14; later 25	44
Gravesen	179	50	31	7	88	1		90
Matson	150	70	36	9	115		1st 8 wk. 9; later 26	35
Kinsella	148	69	21	9	99		1st 8 wk. 20; later 29	49
Hegner	111	36	32	10	78		1st 8 wk. 19; later 14	33
Lambert and Berry	100	27	21	7	55	5	Post-op. 24; later 16	40
Eloesser	100	34	9	10	53	22	1st 8 wk. 3; later 22	25
Casper and Bruns	92	26	21	4	51		1st wk. 8; 2d wk.–3d mo. 13; later 20	41
Archibald	78	20	35	0	55		1st 8 wk. 6; later 17	23
Alexander	78	32	4	19	55		1st 8 wk. 17; later 6	23
Jessen	69	34	12	11	57		1st 8 wk. 8; later 4	12
Davies	46	14	6	10	30		1st 8 wk. 5; later to 4th yr. 11	16
Eizaguierre	41	9	9		18		1st 12 wk. 4; 12 wk. to 1 yr. 6; later 13	23
Beye	38	18	11	1	30		1st 8 wk. 5; later 3	8
Sachs	36	19	9	1	29		1st 2 wk. 4; 3d wk. to 2 yr. 3	7
Piotet and Eureh	31	2	16		18	7	1st 3 wk. 4; 7 mo. to 2 yr. 2	6
Dolley	26	22	1		23		1st 8 wk. 2; later 1	3
Bettman	20	14	1		15		1st 8 wk. 3; later 2	5
Totals	2,523	840	665	158	1,653	83		787
Per cent		33.5	25.9	6.2		3.3		31.1

10–20 per cent; Geer, 75 cases, operative deaths during 2 months, 9–16 per cent, later deaths from progress of the tuberculosis 24 per cent, "not doing well" 24 per cent, well 30–40 per cent; Piotet and Eureh operating through a special incision had a 13 per cent operative mortality, two died later, 65 per cent greatly improved or cured during a period of 1 to 7 years' observation; Johns, 100 cases; Maurer and Rolland, 42 cases with 3 deaths in third week; Wangenstein, 61 patients with 10 hospital deaths.

TABLE 16

Summary of all cases

	TOTAL CASES	GROUP					UNKNOWN 5	DEAD			
		1	2	3	4	Total		1st 8 wks.	2–12 mos.	1–14 yrs.	Total
Table 14.....	1,239	492	180	52	7	731	51	150	113	194	457
Table 15.....	2,523	840	655	158	0	1,653	83				787
Total.....	3,762	1,332	835	210	7	2,384	134				1,244
Per cent....		35.4	22.1	5.5	0.2		3.5				33.0

The degree of rehabilitation of the patients who are clinically cured is attested by the fact that a large proportion of the patients are able to, and do, resume their former occupation or lead the kind of lives they did previous to their illness. Among my own patients table 17 shows a list of the occupations in which they are now employed.

TABLE 17

Occupations of patients rehabilitated by thoracoplasty

Housewife.....	23	Farmer.....	2	Politics.....	1
Detective.....	1	Nurse.....	1	Saleslady.....	2
School teacher.....	2	Bank clerk.....	1	Laborer.....	4
Housework.....	6	Business.....	15	Chemist.....	1
Clerk.....	5	Maid.....	1	Dentist.....	2
Attorney.....	2	Cashier.....	1	Hotel clerk.....	1

One of my patients developed extensive pneumonia a year after operation, from which she entirely recovered. The use of an oxygen tent is believed to have contributed to her recovery. One had a nephrectomy for tuberculosis of the kidney; one, a colored woman, had a hysterectomy for fibroids. All of these patients have remained well. Several of the

patients have married since their recovery and one has recently given birth normally to a baby and both mother and child are well.

Bull records 10 pregnancies with the birth of living infants in seven, but three of the babies died within a few weeks of birth; and one died at the age of 8 years from measles and acute meningitis. Three have remained well, and one is seven years of age. One patient died during the 8th month of her pregnancy. Jessen, Lambert and Miller, Berard and Dumarest, and Haymaker each records one. Hofbauer reports one woman who had a baby and who remained well for a period of 8 years after operation. Bush records two, one of whom at the time of childbirth had a persistent fistula from an empyema complicating the pulmonary lesion. Kinsella has 6 "thoracoplasty babies" in his series, two of three mothers having had two babies each since operation, all women remaining well. One woman reported by Saye had a thoracoplasty during a third pregnancy, went to term, and had a normal baby.

Among a few discordant notes as to the results of thoracoplasty may be mentioned the reports of Orszagh, who records 29 deaths among 66 cases; and of Wiener and Fishberg, who had 9 per cent postoperative and 30 per cent later deaths, 15.9 per cent still in the hospital 2 to 10 years after operation, while 31.8 per cent were still under treatment in clinics and not able to work because of active or chronic tuberculosis. Thirty-four of 44 who survived received no benefit from the operation; some bled after operation who did not bleed before; the idea of thoracoplastic closure of cavities they consider "illusory." Of 10 patients with empyema who had thoracoplasty four were dead, two still in the hospital very ill, three still had draining sinuses, and one was well enough to work. In commenting on this report which is so utterly divergent from those reviewed it may be said that, while there is no reason to doubt that these authors' experience is as they state, it seems to be unique. Furthermore, even though it is difficult to prove in any given case of tuberculosis treated by thoracoplasty that the patient might not have got well without it this cannot be said of tuberculous empyema.

PARTIAL THORACOPLASTY

Partial thoracoplasty may be defined as consisting of the resection of longer or shorter segments of 7 ribs or less. It may involve the first two stages of an ordinary three-stage thoracoplasty or the resection of very long segments of the upper ribs only, including the full length of the upper one or two. Such a resection, resulting in a drop of the apex of

the pleural cavity to below the level of the clavicle in front and the fourth rib behind, has for several years been performed routinely by the author as a part of the total resection, whenever an extensive collapse seemed indicated particularly for a very large upper-lobe cavity. If the lower part of the lung seemed relatively uninvolved and symptoms subsided and bacilli in the sputum disappeared, the resection was carried no further. In some cases the additional resections of shorter segments of the fifth to the seventh sufficed to make the patient symptom-free. Many other surgeons working in this field have adopted this procedure. In 1928 Graf reported 9 cases operated by this method which he called "selective thoracoplastic collapse" with very good results, and in 1930 he writes that he had removed the whole first rib in 40 cases without bad results but through a combined posterior and anterior approach. The author always performs the operation through a low paravertebral incision only, which does not extend around the lower end of the scapula. The secret of an approach is lifting the scapula away from the chest-wall and the use of a lung periosteal elevator.

Loeschcke and Rost limit the resection to the 1st rib, preferably with additional division of all the scaleni. Rost states that Wilms's cases so operated showed 34 per cent of clinical cures. Roux has described a special incision along the 7th rib for resecting the upper seven ribs.

The evaluation of final results of limited partial thoracoplasty is not possible at this time because too few cases have been followed sufficiently long to establish them. Comparisons of results are also impossible because of lack of details in most reported series as to the extent of the resection. Late results in a few reported series are given in table 18. Of the 236 cases, 87.2 per cent were living and 12.8 dead. Half of the deaths were in the first 8 weeks after operation. Of 175 living, followed more than 2 years, 53 per cent were symptom-free and without bacilli in the sputum.

TABLE 18

Results of partial thoracoplasty

AUTHOR	YEAR	CASES	LIVING					UNKNOWN 5	DEAD		
			1	2	3	4	Total		1st 8 weeks	Later	Total
Dolley	1934	59	49	1	0	4	54	0	2	3	5*
Eloesser	1934	39	14	3	5	11	33	0	1	5	6*
Coryllos	1934	26	23	3	0	0	26	0	0	0	0
Key	1930	20	10	4	2	0	16	0	1	3	4*
Uhlenbruck	1931	17	9	0	5	3	17	0	0	0	0
Hegner	1934	19	6	5	0	0	11	0	7	1	8*
Hegner	1934	18	2	13	0	0	15	0	2	1	3
Jessen	1930	15	9	3	1	0	13	0	1	1	2*
Domanig and Denk	1931	13	2	2	1	6	11	0	1	1	2
Kinsella	1934	10	6	1	3	0	10	0	0	0	0*
Totals		236	130	35	17	24	206		15	15	30

* Two years or more after operation.

Neuhof has added an extrapleural stripping to the partial thoracoplasty in cases with much thickening of the pleura over the cavity. Among 24 cases of partial thoracoplasty there was one death, and 10 were discharged with collapsed cavities and bacilli-free, the others awaiting further operation. Thomsen has done 12 cases without complication.

PNEUMOLYSIS WITH AND WITHOUT PLOMBAGE

Pneumolysis without plombage proposed by Tuffier and adopted successively by Schlange, Mayer and by Jessen was ineffective because too limited. To prevent this Tuffier introduced fatty tissue between the separated lung and chest wall to prevent reëxpansion. Baer, 1913, substituted paraffin and later Archibald used a muscle plastic. The paraffin method of Baer has been generally accepted. The method has also been combined with section of the scaleni, phrenicoexairesis and with thoracoplasty, and the technical procedures and approach vary. Comparative statistics of any large groups of cases of plombage used independently are therefore not available. The individual results in a few series of cases are given in table 19.

TABLE 19

Results of pneumolysis with plombage

AUTHOR	YEAR	CASE	LIVING					UNKNOWN 5	1ST 8 WEEKS	LATER	TOTAL	TIME AFTER OPERATION
			1	2	3	4	Total					
DeWinter....	1932	181	58	8	0	0	66		50	65	115	1–5 years*
Alexander....	1934	43	16	13	0	9	38			5	5	9 months–3 years
Denk and Domanig...		30	4	8	4	0	16	7	4	3	7	
Waitz.....		21	0	20	0	0	20		1	0	1	
Coryllos.....	1934	13	4	5	2	0	11			2	2	
Coryllos.....	1934	7	3	0	0	0	3			4	4	
Eloesser.....	1934	12	1	3	3	3	10			2	2	2 years or more
Totals.....		307	86	57	9	12	164	7	55	81	136	

* Used muscle in 154.

Sauerbruch discusses indications as an independent procedure and secondary to thoracoplasty as used in about 1,000 cases, but does not give results of his experience of plombage used independently.

Dumarest and Rougy report their results of paraffin plombage of cases as follows: excellent 36 per cent, improved 28 per cent, and not improved 36 per cent. Bernou and Fruchaud in 21 cases had satisfactory results in 21; there was a perforation resulting in death in one.

Kremer and Beitz report 52 cases, 22 observed more than 1 year later. Of these 10 became tubercle-bacilli negative; Mantau, 22 with prolonged good results in 7, improved 5, stationary or doubtful 6, worse 2; Walzel in 100 cases obtained good results in 45 per cent; and Waltuch in 15 cases had 9 improved, 4 unimproved, and 2 dead; Winternitz reported 49 cases; Roloff among 42 cases observed ten more than 2 years, of which "two were closed, four open and four died."

PHRENIC-NERVE OPERATIONS

Phrenic-nerve operations are reported in large series for a variety of indications and types of pathological lesions. At one extreme it is done to hasten the convalescence of patients when prognosis is considered good with bed-rest only; at the other extreme it is done as a forlorn hope when the prognosis is bad. Many patients are reported as clinically cured after one or two years' observation, even though it is widely recognized that with so limited a degree of collapse there is a very considerable chance of reactivation even after several years. It is obvious, therefore,

that the evaluation of late results must be made only after a period of years, and that no comparison of results obtained in different clinics is of any value except of the same types of cases treated along parallel lines. Among those of large experience who have reported their results may be mentioned Sauerbruch, who states that enduring clinical cures from the operation as an independent procedure are exceptional. Derscheid and Toussaint (668 cases) report 15 cures, 33 improved, 11 deaths in the first 8 weeks and 35 later. O'Brien in 1930 reported 500 cases, 52.2 per cent of which became bacilli-negative. Nehil and Alexander, on the basis of careful study, report 272 cases, of which 92 were found symptom- and bacilli-free, 95 improved and 33 unimproved, two years or more after operation. Hegner similarly reports 232 cases with 14 clinical cures, 113 improved, and 33 unimproved; Welles, 271 cases, of which 173 were improved and 98 unimproved; Roloff, 231 cases, of which 26.8 per cent were cured after 2 to 8 years and 48.9 per cent had died. Matson states that, of his cases, 15 per cent of the patients who were otherwise candidates for thoracoplasty were spared this operation as a result of the phrenic-nerve operation. Sachs and Jaski and many others report a relatively large proportion of favorable results. Many, on the other hand, are not impressed by the late results of the operation.

COMBINATION OF METHODS

The different methods described, together with phrenic crushing and scaleniotomy, are being used in various combinations. The demonstration that many patients tolerate surprisingly well a partial bilateral pneumothorax has led to the use of the phrenic operation, apicolysis, plombage or limited thoracoplasty on one side, with pneumothorax on the other. A few cases of bilateral plombage and of bilateral apical thoracoplasty are recorded, and a few of one method for one side and another for the opposite side and with some encouraging results. Jessen has studied the relative results of one method and of a combination of methods for unilateral lesions in 300 cases. By the use of one method only, he obtained 59 per cent of good results; 16 per cent with no improvement; 25 per cent total mortality: by a combination of methods, 55 per cent with good results; 22 per cent with no improvement; and 23 per cent mortality.

There can be no doubt that a judicious combination of methods may result favorably in cases in which one method alone will fail.

SUMMARY

The surgical treatment of pulmonary tuberculosis includes paralysis of the diaphragm, division of the scaleni, partial and total posterior and anterolateral thoracoplasty and pneumolysis with plombage, singly and in various combinations. The indications as followed in different clinics and the technical details vary in important respects. Results obtained by different surgeons are therefore not strictly comparable but they do furnish the basis for a perspective of what has been achieved.

This study concerns itself chiefly with total posterior extrapleural thoracoplasty, but includes available reports of partial thoracoplasty and of pneumolysis with plombage. The author's own 200 cases and a number of series totalling 3,672 cases of thoracoplasty reported since 1926, and which give comparable details, furnish the material for it. It includes also 236 cases of partial thoracoplasty and 307 of pneumolysis with plombage. The results are studied with special reference to early and late mortality, causes of death, and duration and degree of improvement or of rehabilitation.

Thoracoplasty

From one-quarter to nearly one-half the deaths within a period of five to ten years occur within the first eight weeks. The author's mortality in this period was 10.3 per cent; the combined mortality among 2,810 cases was 10.5 per cent. The individual variations among the series were from 3 to 20 per cent. The most frequent cause of death in the author's experience was cardiac failure and pulmonary complications. In a combined group of 230 deaths, death was reported to have been due to shock in 8 per cent, heart failure in 18 per cent, and pulmonary complications or extension of tuberculosis in 34 per cent. The mortality rate decreases progressively after the first few weeks. From one-half to two-thirds die during the first 6 months.

Among 3,762 patients followed for from one to twelve years after operation, 35.3 per cent were symptom- and bacilli-free and were able to work; 22.1 per cent were improved and able to do some work; 5.5 per cent were not improved or were made worse by the operation; 3.5 per cent were not traced; and 33.6 per cent were dead at the time of the report. A large proportion of the patients are rehabilitated to the extent that they are able to return to their former stations in life and to resume their former occupation or activities. Many women marry, and there

is record of 22 who have borne children since their operation, usually against advice.

The variation in extent of partial thoracoplasty and the relatively limited number of any one type followed for one or more years make any estimate of enduring results from them inconclusive. Among 236 collected cases followed for two years or more, 87.5 per cent were living, and 12.5 per cent were dead. Of the living, 53.4 per cent were reported as clinically well; of the deaths one-half occurred during the first eight weeks after operation.

Pneumolysis and plombage

Of 307 cases observed during several months to several years, 53.4 per cent were clinically well, 18.5 per cent were improved, and 44.3 per cent were dead. Of the deaths, 40 per cent occurred during the first 8 weeks after operation.

Phrenicoexairesis as an independent procedure

This operation is performed for such a variety of indications and the chance of later recurrence of the disease following so limited a collapse is so considerable that prolonged observation of the patients in any one group will be necessary for a determination of late results. The results so far reported are conflicting, but a considerable number of enduring clinical cures are recorded.

A combination of methods has extended indications to include cases with bilateral lesions and has improved results.

CONCLUSIONS

The surgical treatment of pulmonary tuberculosis offers to properly selected patients not suitable for pneumothorax therapy the best if not the only prospect of a complete arrest of the disease and, when that cannot be achieved, of relief of symptoms and prolongation of life.

The proper selection of the patients and of methods and of the most opportune time for operation demands the closest collaboration of the phthisiotherapist and surgeon.

From one-quarter to one-half of the total deaths during the first ten years following thoracoplasty occur during the first 8 weeks and death is due largely to shock, cardiac failure, and pulmonary complications, all in considerable measure preventable through preoperative preparation, through operation graded into stages according to the patient's condi-

tion, and watchful prolonged postoperative supervision. Such measures will extend indications for operation. Even though by so doing the total mortality is not reduced, more patients otherwise hopeless are given the chances it affords.

Deaths after the first 8 weeks are due largely to extension of the tuberculosis, in some measure preventable through primary adequate collapse, through secondary additional collapse or compression for recurrence and through reasonable care of the health.

Adequate application of the method or combination of methods indicated, early in the disease before extensive destructive changes in the lung and before secondary visceral damage has occurred, will result in a minimal mortality, a maximal conservation of respiratory function, and in the greatest possible measure of rehabilitation.

BIBLIOGRAPHY

ALEXANDER, J.: Personal communication, 1934.

ALLEN, D. S.: Bilateral partial thoracoplasty for bilateral tuberculosis, J. Thorac. Surg., 1932, i, 587.

ARMAND-DELILLE AND DEVELAY: Collapse therapy in children: results, Bull. Soc. Pediat., Paris, 1930, xxviii, 599.

BABCOCK, W. W.: Carotid-jugular anastomosis in the treatment of advanced pulmonary tuberculosis, Surg. Clin. North America, 1929, ix, 1047.

BAER, G.: Paraffin filling: results of 19 years of experience, Ztschr. Tuberk., 1932, lxiv, 319.

BARNES, H. L.: Extra-pleural thoracoplasty in phthisis: results in 12 cases, Rhode Island M. J., 1933, xvi, 37.

BETTMAN, R. H.: Personal communication, 1934.

BERARD, L.: Apicolysis: critical study and indications, Arch. Méd. Chir. l'App. Respir., 1932, vii, 511.

BERARD, L., AND DELGOFFE, A.: Eleven years' practice of thoracoplasty in urban hospital service, Ibid., 1932, vii, 1.

BERARD, L.: Resection of first ribs and apicolysis without plugging: case, Lyon Chir., 1932, xxix, 208.

BERARD, L., AND GUILLEMINET, M.: Technic and results of phrenicectomy, Bull. l'Acad. Méd., 1929, ci, 792.

BERNOU, A., AND FRUCHAUD, H.: Plugging in bilateral tuberculosis, Rev. Tuberc., 1932, xiii, 726.

BERNOU, A., AND FRUCHAUD, H.: Partial thoracoplasty with apicolysis and apicolysis with plugging, Arch. Méd. Chir. l'App. Respir., 1932, vii, 559.

BEYE, H. L.: Personal communication, 1934.

BRAUER, L.: Scientific foundations of collapse therapy, Deutsche med. Wchnschr., 1933, lix, 825.

BRAUN, P. V., AND ELOESSER, L.: Lung compression and surgery of lung for relief of tuberculosis, California and Western Med., 1927, xxvi, 335.

BREMER, H., AND UHLENBRUCK, P.: Clinical use of Lauwer method of treating apical processes by means of apicolysis, Ztschr. Tuberk., 1931, lxiii, 1.

BROCK, J., AND SAUER, W.: Thoracoplasty in children, Ztschr. f. Kinderhk., 1928, xlvi, 703.
BRONFIN, I. D.: Indications for collapse therapy, Ann. Int. Med., 1933, vii, 468.
BROWN, A. L., AND ATKINSON, K. J.: Evaluation of scaleniotomy accompanying phrenic evulsion, Amer. Rev. Tuberc., 1933, xxviii, 176.
BRUNS, E. H., AND CASPER, J.: Thoracoplasty in chronic pulmonary tuberculosis, Ibid., 1930, xxii, 739.
BRUNS, E. H., AND CASPER, J.: Present status of chest surgery, with special reference to thoracoplasty, Ibid., 1932, xxvi, 665.
BULL, P.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 261.
BUSCH: Thoracoplasty in relation to labor, Beitr. Klin. Tuberk., 1930, lxxiv, 223.
CARLSON, H. A., BALLON, H. C., WILSON, H. M., AND GRAHAM, E. A.: Phrenicectomy: effect upon cough and expectoration: study based upon elimination of lipiodol (iodized oil) and foreign bodies from lungs, J. Thorac. Surg., 1933, ii, 573.
CARTER, B. N.: Thoracoplasty; 53 cases, Arch. Surg., 1931, xxii, 289.
CARTER, B. N.: Personal communication, 1934.
CARYOPHYLLIS, H. P.: Collapse therapy: direct results, Wien. klin. Wchnschr., 1931, xliv, 1467.
CHURCHILL, E. D.: "Strain" on collateral lung in collapse therapy, Arch. Surg., 1929, xviii, 553.
CLYNE, M.: Scaleniotomy: preliminary report, Amer. Rev. Tuberc., 1932, xxvi, 771.
CORYLLOS, P. N.: Personal communication, 1934.
COURCOUX AND BERNOU: Association of thoracoplasty and pneumothorax, Rev. Tuberc., 1932, xiii, 569.
CURSCHMANN, W.: Evaluation of results in treatment of pulmonary tuberculosis, Beitr. Klin. Tuberk., 1930, lxxiv, 321.
DAVIES, H. M.: Phrenic avulsion in pulmonary tuberculosis, British M. J., 1926, i, 315.
DAVIES, H. M.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 370.
DAVIES, H. M.: Thoracic surgery, Lancet, 1933, ccxxiv, 511.
DECKER, H. R.: Phrenic-nerve operation: results in 222 cases, with discussion of technic of operation, J. Thorac. Surg., 1933, ii, 538.
DENK, W.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 406.
DENK, W., AND DOMANIG, E.: Surgical treatment of pulmonary tuberculosis, Beitr. Klin. Tuberk., 1931, lxxvii, 320.
DERSCHEID, G., AND TOUSSAINT, P.: Results of thoracoplasty and phrenicectomy, Arch. Méd. Chir. l'App. Respir., 1932, vii, 588.
DERSCHEID, G.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 410.
DEWINTER, L., AND SEBRECHTS, J.: Arch. Méd. Chir. l'App. Respir., 1932, 377.
DIVIS, J.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 434.
DOLLEY, F. S.: Personal communication, 1934.
DUMAREST, F.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 366.
DUNHAM, K., AND ASBURY, E.: Thoracoplasty: general and economic considerations, Jour. Am. Med. Ass., 1932, xcix, 360.
DUNNER, L.: Exairesis of phrenic nerve, Ztschr. Tuberk., 1927, xlix, 31.
DUVAL, P., QUENU, J., AND WELTI, H.: Extrapleural thoracoplasty by way of axilla, Jour. Chir., 1930, xxxii, 641.

EIZAGUIERRE, E.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 414.

ELS, H.: Report of successful results in cases of unilateral pulmonary tuberculosis, Zentralbl. f. Chir., 1930, lvii, 2228.

EHRENFRIED, A.: Surgical measures in treatment of lung tuberculosis, Am. Jour. Surg., 1931, xii, 95.

ELOESSER, L.: Personal communication, 1934.

ELVING, H.: Resection of scalene muscles together with two highest ribs in pulmonary tuberculosis, Finska Läk-Sällsk. Handl., 1931, lxxiii, 772.

FALTIN, R.: Thoracoplasty in pulmonary tuberculosis, Ibid., 1928, lxx, 1088.

FELIX, W.: Extrapleural plugging, Ztschr. Tuberk., 1931, lix, 385.

FISHER, L.: Scaleniotomy as adjunct to collapse therapy, Amer. Rev. Tuberc., 1932, xxvi, 776.

FRANGENHEIM, P.: Apicolysis for apical tuberculosis technic, Arch. klin. Chir., 1930, clxii, 674.

FREUND, A.: Bilateral collapse therapy, Ztschr. Tuberk., 1931, lxi, 203.

FRUCHAUD, H.: Technic of apicolysis with paraffin plugging, Rev. Tuberc., 1933, i, 225.

GALE, J. W., AND MIDDLETON, W. S.: Scaleniotomy, Arch. Surg., 1931, xxiii, 38.

GAINES, A. R., AND KELLER, P. E.: Collapse therapy in Negroes, Amer. Rev. Tuberc., 1933, xxviii, 779.

GEER, E. K.: Justification of collapse therapy, Journal-Lancet, 1932, lii, 353.

GILBERT, M., AND FROEHLICH, W.: Apicolysis with paraffin plugging, Schweiz. med. Wchnschr., 1933, lxiii, 613.

GJESSING, M. H.: Experiences with thoracoplasty in pulmonary tuberculosis, Norsk. Mag. f. Laegevidensk., 1928, lxxxix, 933.

GRAF, W.: Resection of entire first rib in extrapleural thoracoplasty and possibility of an isolated removal of rib from apical upper fields ("Thoracoplastic selective collapse"), Deutsch. med. Wchnschr., 1930, lvi, 1647.

GRAF, W.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 403.

GRAHAM, E. A., AND ALLEN, D. S.: Operations and demonstrations of cases in Barnes Hospital: thoracoplasty and phrenicotomy, Arch. Surg., 1929, xix, 1545.

GRAVESEN, J.: Results of thoracoplasty in phthisis, Lancet, 1926, xi, 702.

GRAVESEN, J.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 301.

GRAVESEN, J.: Ein mit doppelseitiger partieller Thorakoplastik behandelter Fall, Ztschr. Tuberk., 1932, lxvi, 53.

GUCCI, G.: Experimental ligation of pulmonary vessels; relation to surgical therapy, Policlinico (sez. chir.), 1932, xxxix, 697.

HANKE, H.: Die kavernöse Lungentuberkulose und ihre Beeinflüssung durch chirurgische Massnahmen (ausschliesslich Pneumothorax und Eingriffe innerhalb des Pleuraraumes), Beitr. Klin. Tuberk., 204–219.

HARMS AND GRUNEWALD: Loeschcke-Rost operation for pulmonary tuberculosis, Ibid., 1930, lxxiv, 316.

HAUKE, H.: Surgical treatment of circumscribed tuberculosis of upper lobe, Arch. klin. Chir., 1931, clxvii, 582.

HEGNER, C. F.: Surgery of pulmonary tuberculosis, Colorado Med., 1927, xxiv, 34.

HEGNER, C. F.: Personal communication, 1934.

HELLSING, G.: Thoracoplasty in pulmonary tuberculosis, Acta Med. Scand., 1929, lxxi, 521.

HEYMER, A., AND THALER, W.: Thoracoplasty: possibility of permanent cure and operability, Ztschr. Tuberk., 1932, lxiv, 427.

HUBER, P., AND WAITZ, C.: Collapse therapy, thoracoplasty phrenic exairesis, partial plastic surgery, paraffin plugging, Beitr. Klin. Tuberk., 1932, lxxx, 139.

HUDSON, B.: Two remarkable cases of large cavities closed by surgical methods, Tubercle, 1933, xiv, 548.

JACOBAEUS, H. C.: Indications for different operation in surgical treatment of pulmonary tuberculosis, Amer. Rev. Tuberc., 1928, xviii, 94.

JESSEN, F.: Childbirth following thoracoplasty, Ztschr. Tuberk., 1929, liii, 214.

JESSEN, H.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 395.

JESSEN, H.: Thoracoplasty in bilateral tuberculosis, Beitr. Klin. Tuberk., 1933, lxxxi, 672.

JESSEN, H.: Combination collapse therapy, Verhandl. d. Deutsch. Gesellsch. f. inn. Med. Kong., 1932, xliv, 181.

JOHNS, F. S., AND COLE, D. B.: 8 years of selective collapse, J. Thorac. Surg., 1933, ii, 247.

JULLIEN, W., ECOT, F. C., AND MOLLARD, H.: Thoracoplasty in patient treated with double pneumothorax, Rev. Tuberc., 1933, i, 173.

KASSOWITZ, V. E.: Evaluation of surgical treatment in pulmonary tuberculosis, Wisconsin Med. Jour., 1926, xxv, 279.

KERSCHNER, F.: Die Ligatur der Vena Cava bei Lungen-Tuberkulose, Ztschr. f. Tuberk., 1931, lx, 198.

KEY, E.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 385.

KINSELLA, T. J.: Personal communication, 1934.

KIRSCHNER: Thoracoplasty; method of minimizing injurious effects on respiration and circulation by predetermining degree of constriction of thorax, Arch. klin. Chir., 1931, clxvii, 557.

KLEESATTEL, H.: Total resection of first rib, Beitr. Klin. Tuberk., 1933, lxxxii, 571.

KLOPSTOCK, R.: Bilateral collapse therapy (thoracoplasty of one side with simultaneous pneumothorax of opposite side), Ztschr. Tuberk., 1931, lxi, 14.

KOCHS, ELS AND JUNKERSDORF: Phrenic exairesis: experimental attempts to improve results by resection of scalenus muscles, Beitr. Klin. Tuberk., 1930, lxxv, 772.

KRAUSE, A. K.: Human resistance to tuberculosis at various ages of life, Amer. Rev. Tuberc., 1925, xvi, 191.

KREMER, W., AND BEITZ, J.: Anfangrsultäte nach Oberlappenplombierung, Ztschr. Tuberk., 1932, lxvi, 177.

LADECK, E.: Thoracoplasty on one side with pneumothorax in opposite lung, Ibid., 1931, lxi, 18.

LAMBERT, A. V. S., AND BERRY, F. B.: Extrapleural thoracoplasty, Ann. Surg., 1930, xci, 57.

LILIENTHAL, H.: Sequence in two-stage thoracoplasty, Arch. Surg., 1927, xiv, 362.

LINDBERG, D. O. N.: Phrenic neurectomy; secondary diaphragmatic rises following operation, Amer. Rev. Tuberc., 1933, xxviii, 352.

LOESCHCKE, H., AND ROST: Surgical therapy in pulmonary tuberculosis, Deutsch. Ztschr. f. Chir., 1930, ccxxvii, 491.

MAENDL, H.: Successful artificial pneumothorax on right side after unsuccessful pneumothorax, phrenic exairessi and thoracoplasty on left side, Wien. klin. Wchnschr., 1929, xxv, 1664.

MANTAU: Apicolysis (Lauwer Method) in apical tuberculosis, Ztschr. Tuberk., 1933, lxviii, 323.

MATSON, R. C.: Personal communication, 1934.

MATSON, R. C.: Collapse therapy (phrenic neurectomy) in the treatment of pulmonary tuberculosis, Western Jour. Surg., 1930, xxxviii, 743.

MATSON, R. W.: Phrenicotomy, Tr. Nat. Tuberc. Assn., 1928, xxiv, 170.

MAURER, A., AND ROLLAND, J.: Present status of problem of surgical treatment of pulmonary tuberculosis, Paris Méd., 1930, i, xix.

MORIN, CARDES AND PICOT: Immediate results in 14 thoracoplasties in pleuro-pulmonary tuberculosis, Rev. Méd. Suisse Rom., 1928, xlviii, 999.

NAEGELI, T., AND SCHULTE-TIGGES, H.: Phrenicoexairesis; rôle among other surgical methods of treatment, Ztschr. Tuberk., 1933, lxviii, 29.

NEDDERMEYER, A., AND WALTHER, G.: Phrenic exairesis in pulmonary tuberculosis, München. med. Wchnschr., 1931, lxxviii, 476.

NEHIL, L. W., AND ALEXANDER, J.: Phrenic nerve interruption: estimate of value based upon 654 cases, J. Thorac. Surg., 1933, ii, 549.

NEUHOF, H.: Investigation and operative exploration and treatment of old tuberculous cavitation, with special reference to pneumonocavernolysis, Amer. Rev. Tuberc., 1933, xxviii, 344.

NEUMANN, W.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 409.

NEUMANN, W.: Available methods of collapse therapy, Wien. klin. Wchnschr., 1931, xliv, 1539.

NISSEN, R.: Der operative Verschluss von grossen bronchial Fistulae. "Gitterlungen" und durchgebrennen Tuberkulosen, Deutsch. Ztschr. Chir., 1932, ccxxxvi, 573.

NYSTROM, G., AND BESKOW, A.: Surgical treatment of pulmonary tuberculosis, Upsala läkaref. Förh., 1930, xxxv, 41.

O'BRIEN, E. J.: Personal communication, 1934.

O 'BRIEN, E. J.: Collapse therapy in early minimal lesions, Am. J. Roentgenol., 1933, xxx, 315.

ORSZAGH, O.: Thoracoplasty in the treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 374.

O'SHAUGHNESSY, L.: Surgical treatment of pulmonary tuberculosis, Lancet, 1933, ccxxiv, 443.

PETERS, L. S.: Treatment of cavities in pulmonary tuberculosis, Ann. Int. Med., 1932, vi, 802.

PHILLIPS, E. W.: Thoracoplasty in tuberculosis, Southwestern Med., 1927, xi, 213.

PIOTET, G., AND EUREH: Immediate and end results of thoracoplasty in pulmonary tuberculosis.

PLIENINGER, T.: Die chirurgische Behandlung der hilusnahen Kaverne, Beitr. Klin. Tuberk., 1932, lxxx, 291.

REHN: Extensive partial plastic operation in tuberculosis of upper lobe, excluding danger of aspiration, Ztschr. ärztl. Fortbild., 1932, xxix, 285.

ROESLER, G.: Late injuries after phrenic exairesis, Deutsch. med. Wchnschr., 1931, lvii, 937.

ROGERS, W. L.: Extrapleural paraffin filling in thoracic surgery; "Paraffin Plombierung," Amer. Rev. Tuberc., 1931, xxiv, 636.

ROLOFF, W.: Dauererfolge der Lungenkollapsbehandlung, Statisticher Bericht über 1128 Fälle aus den Jahren 1918, 1928.

SACHS, W.: Artificial paralysis of diaphragm in pulmonary tuberculosis, Beitr. Klin. Tuberk., 1930, lxxiv, 284.

SAUERBRUCH, F.: Chirurgie der Brustorgane, ed. 2, 1930.

SAUERBRUCH, F.: The surgical treatment of pulmonary tuberculosis, Seventh conference de l'union internationale contre la tuberculose, 1930, 354.

SCHEDTLER, O.: Statistics on results of extrapleural thoracoplasty, Deutsch. med. Wchnschr., 1931, lvii, 491.

SCHNIPPENKOTTER, W.: Surgical paralysis of the diaphragm, Beitr. Klin. Tuberk., 1926, lxv, 56.

SCHULTE-TIGGES, H.: Statistics of the treatment of pulmonary tuberculosis, Deutsch. med. Wchnschr., 1932, lviii, 772.

SCHWATT, H.: Bilateral phrenic exairesis in pulmonary tuberculosis, Amer. Rev. Tuberc., 1933, xxviii, 165.

SERGENT, E.: Paralysis of phrenic nerve in cancer of lungs and in pulmonary tuberculosis, Bull. et Memo. Soc. Méd. Hóp. Paris, 1930, liv, 7.

SHOYAMA, S.: Amazing healing of cavernous lungs following thoracotomy and pneumolysis: case, Zentralbl. Chir., 1932, lix, 2644.

SLAVIN, P.: Closure of adherent cavities by combined artificial pneumothorax and phrenicectomy, Amer. Rev. Tuberc., 1933, xxvii, 355.

SONNENFELD, A.: Indications for phrenic exairesis alone and combined with pneumothorax, Beitr. Klin. Tuberk., 1928, lxix, 340.

STUB-CHRISTENSEN: Phrenicectomy in surgical treatment of pulmonary tuberculosis, Hospitalstid, 1929, lxxii, 1297.

SUNDBERG, R. H.: Phrenic neurectomy in tuberculous empyema, Amer. Rev. Tuberc., 1931, xxiii, 46.

THEARLE, W. H.: Radical phrenicotomy for pulmonary tuberculosis; Jour. Amer. Med. Assn., 1926, lxxxvi, 811.

THEARLE, W. H.: Personal communication, 1934.

THOMSEN: Die erweiterte ober Teil-Plastik bei Lungen-Tuberkulose und ihr Instrumentarium, Beitr. Klin. Tuberk., 1929–1930, lxxix, 656.

ULRICI, H.: Collapse therapy types and results, Klin. Wchnschr., April 9, 1932, xi, 643.

ULRICI, H.: Thoracoplasty of apical processes, Deutsch. med. Wchnschr., 1932, lviii, 411.

WALZEL, P.: Phrenicotomy and collapse treatment of pulmonary tuberculosis, Wien. med. Wchnschr., 1930, lxxx, 251.

WANGENSTEIN, O. H.: Rôle of surgery in tuberculous control, Jour. Lancet, 1932, lii, 241.

WELLES, E. S.: Phrenicectomy in 300 cases of pulmonary tuberculosis, Arch. Surg., 1929, xix, 1169.

WERNER, W. I., AND O'BRIEN, E. J.: Effect of phrenicectomy on cavitation, Am. Jour. Roentgenol., 1930, xxiv, 626.

WHITE, P. D.: Relationship of the heart and lungs in disease, Arch. Surg., 1929, xviii, 339.

WHITTEMORE, W.: Thoracoplasty, New England J. Med., 1932, ccvii, 211.

WIENER, J. J., AND FISHBERG, M.: Ultimate results of thoracoplasty operations, Arch. Int. Med., 1933, lii, 341.

WIESE, O.: Present status of pulmonary collapse therapy during childhood, Ztschr. f. Tuberk., 1931, lx, 406.

WINTERNITZ, A.: Paraffin plugging, Deutsch. Ztschr. Chir., 1932, ccxxxv, 752.

WIRTH, A., AND KOHN VON JASKI, G.: Experiences with 600 operations on phrenic nerve, Beitr. Klin. Tuberk., 1929, lxxiii, 1.

WOLF, J. E., AND LOSSEN, H.: Phrenicectomy in cavernous phthisis of upper lobe, Ibid., 1927, lxvi, 719.

WUNDERLY, H. W.: Collapse therapy, M. J. Australia, 1932, i, 74.

ZAAIJER, J. H.: Results of thoracic surgery, Arch. klin. Chir., 1931, clxvii, 540.

ZIEGLER, O.: Extrapleural thoracoplasty, Deutsch. med. Wchnschr., 1926, lii, 567.

APICAL THORACOPLASTY

FRANK S. DOLLEY[1]

After medical and less radical surgical methods have been thought insufficient or proved unsuccessful, then thoracoplasty is considered.

In advancing caseating tuberculosis it seldom, if ever, has aided in a cure. Thoracoplasty is primarily for chronic pulmonary tuberculosis in which there is cavitation, with sclerosis or a definite tendency towards sclerosis.

As recently as two years ago, the following were usually considered reliable as requisites for thoracoplasty:

1: The patient should not be older than 45.
2: The risk was much increased if he had been tuberculous more than five years.
3: His mediastinum should be rigid.
4: He should have little evidence of myocardial damage.
5: His disease must be unilateral.

If all these requirements were satisfied, then an 11-rib thoracoplasty of comparatively short rib-sections was done. When the last rib section was removed and the wound was closed, the patient's surgical episode was ended. If the result was good, he recovered; if not, the phthisiologist, with varying degrees of philosophy and patience, continued on with the care made definitely more difficult for the doctor and the patient by this final disappointment.

As we look in retrospect on these criteria of scarcely 24 months ago, the improvements of to-day: (1) in end-results; (2) in the reduction in mortality; (3) in the extension of the scope of surgical risks; and (4) in the reduction in lung sacrifice are most dramatic.

The series of 120 patients treated by extensive apical thoracoplasty, which we are about to review critically, will differ little from many others throughout the country. While our conclusions are based on our own people, yet, they reflect with sufficient accuracy the present results obtained by many men dealing with upper-lobe tuberculous cavitation.

As has been said, it is more firmly believed than ever before that

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thoracoplasty will not cure advancing pulmonary tuberculosis, yet, with this exception, all other limitations have been extended.

1: Persons over 45 are not necessarily inoperable; two patients in this series were 58; one was 63; a number were over 50.
2: A long history of tuberculous suppuration does not always preclude operability.
3: A movable mediastinum has not prevented extensive apical collapse, if all other procedures have proved unsuccessful or inadvisable.
4: Myocardial damage *per se* has had an influence only by reducing the amount of collapse at each stage and increasing the number of stages, thus increasing very gradually the resistance offered to the flow of blood from the right to the left heart following lung collapse.
5: Contralateral lung cavitation with extensive sclerosis in the upper lobe does not exclude thoracoplasty, provided there be no definite activity on that side.

The reasons for these far-reaching changes are manifest:

1: When formerly 5–7 ribs were removed at a stage, it is now more often than not 3–4 rib sections that are excised,—occasionally even 1 or 2, if the risk seems considerable.
2: Formerly rib regeneration has required that the intervals between stages be not more than two weeks. Now, by treating the rib periosteum, long intervals can be allowed the patient for recovery between stages, without sufficient stiffening of the chest-wall to greatly interfere with successful collapse.

The night before operation, the patient is given 3 gr. of sodium amytol, the following morning 3–6 gr. more, and ½ hr. before the operation pantopon, gr. ⅓. Atropine is never given since we feel its tendency to make more viscid the bronchopulmonary secretions increases definitely both the danger of postoperative massive atelectasis and to have partially raised thick mucopurulent material fall across both main bronchi at their bifurcation with resultant asphyxia. Surely, many postoperative deaths each year, diagnosed as acute cardiac dilatation or embolus, are due rather to this manner of suffocation. In this series no such accidents occurred.

Gas and oxygen or ethylene is the anaesthetic of choice, although occasionally only novocaine is used. The incision for the upper ribs is the same as for the early posterior thoracoplasty when but short sections were removed. Early in our series, we divided the levator scapulae muscle and began the skin incision just below the trapezial ridge. Now, in men the incision is begun about 5 cm. below the ridge and in women

about 10–12 cm. With the latter the upper extremity of the scar is low enough on the back so that the ordinary dress without neck does not reveal it. The skin above is then extensively undermined and raised by an assistant during the operation. We do not now divide the levator scapulae. Ample exposure of the ribs is obtained by extending the lower end of the wound somewhat anteriorly to the inferior angle of the scapula.

Usually the third rib is removed first since after its resection the approach to the 2nd and 1st is much easier. The third rib is cleared of its periosteum for a distance of 8–10 cm. from its corresponding transverse process, and a section of it is removed. Then the proximal end of the distal fragment is grasped with a heavy haemostat and the remaining portion freed by gently stripping the periosteum off with a flat raspatory, either actually to the costal cartilage or nearly so. In the same manner all of the 2nd and 1st ribs are excised to their cartilages at the sternum, not infrequently the 1st-rib cartilage also. Occasionally, the subclavian vessels lie in a particularly deep groove on the upper surface of the first rib, but by taking care in pushing the periosteum free, the vessels readily retract out of danger at this point. Then as a rule, the fourth rib is extensively excised, though, after completing the upper three, we always make sure that the patient is still in good condition and has only moderate paradoxical motion at this time, since the lung collapse and the paradoxical motion following the removal of the first three is increased approximately 50 per cent following the extensive resection of the fourth. Marked paradoxical respiration may disastrously reduce an already low vital capacity.

The periosteum forming the rib-beds, as well as the rib-ends themselves, are painted with 10 per cent formalin, over the use of which we are most enthusiastic. We feel that this enthusiasm is justified for two reasons:

1: During the ten months since its use, we have had but 3 wound infections,—all slight. The disaster following the first-stage thoracoplasty of a severe infection in the wound, through which we must again enter for further rib resection, has therefore, been spared us, and
2: It markedly inhibits bone regeneration.

In our series there were many patients who from advanced age or debility from chronic suppuration were following the first stage not in condition for other stages for 4–8 weeks. The formalin made these de-

lays of little moment; whereas, without it, rib regeneration would have prevented successful collapse.

The wound is closed without drainage and usually dressed first on the fifth day.

Routinely, glucose is given intravenously after return to bed; frequently, a blood transfusion.

We have performed the above-described extrapleural apicolysis or extensive upper-thoracic-rib resection upon 120 patients. As regards age:

38 were 20–30 years old
41 were 30–40 years old
29 were 40–50 years old
8 were 50–55 years old
1 was 56 years old
2 were 58 years old
1 was 63 years old
There have been no deaths either early or late among those over 45.

When the disease seemed well limited to activity within cavities we held the condition fibroid tuberculosis. If there was evidence of parenchymal activity, it was felt to be fibrocaseous. Under this division:

73 showed fibrocaseous involvement
47 essentially fibroid

In 28 there was involvement in the contralateral lung, which we concluded was inactive. In 8 there was definite activity in the infraclavicular region of the opposite side. The extent of the involvement varied greatly:

22 showed extensive involvement throughout the entire operative side
9 showed extensive involvement of the upper lobe
19 a cavity from apex to the 4th rib posteriorly
50 a cavity or cavities to the 5th rib
11 a cavity or cavities to the 6th rib
9 a cavity or cavities to the 7th rib

For some time, by analyzing postoperative results with the pre-operative X-ray films, we have tried to decide the probable cavity closure difficulties that we might expect to encounter in future similar cases. We consider

1: The probable mediastinal resistance to chest-wall collapse and cavity closure. If there is a definite sustained history of extensive inflammation in the mediastinal half of the involved lung the mediastinal structures are probably rigid. If, however, there is little involvement contiguous to the mediastinum and especially if the trachea is pulled definitely toward the involved side, we are apprehensive concerning complete cavity obliteration, since, with rib resection, the upper mediastinal structures tend to slip mesially taking the mesial wall of the cavity with them.

2: If the cavity wall is apparently thick or if there are many small cavities with shadows suggesting considerable fibrous tissue between them, we feel that our prognosis for initial complete closure should be guarded. On the other hand, a single large cavity, whose lateral wall is adherent to the chest and is mesially supported by considerable scar-tissue, offers a good prognosis.

3: The closer the mesial wall of a cavity is to the shadow of the sternum or vertebral bodies, the more difficult is it to obtain complete obliteration.

4: As a routine, we now locate our cavities by X-ray to determine their distance from both the anterior and posterior chest-walls. The more central we find a paramediastinal cavity, the more difficult we have found it to obtain complete closure.

If the mesial cavity wall is close to the mediastinum or bids fair to fall into a paramediastinal position, we remove all transverse processes. If a cavity-slit still remains, we resect through an anterolateral incision the costal cartilages.

There have been eight infections in this series, three of which made secondary operations necessary. No severe infection has occurred since the use of 10 per cent formalin.

There were 5 immediate deaths. One occurred on the table without warning after completion of a three-rib operation in a patient who until the moment of death was apparently in good condition. We felt the death to have been embolic. Two others, one the second and the other the fourth day post-operative, suddenly died (we felt) from embolus. The fourth died from a complete cardiopericardial synthesis that was not recognized before operation. The fifth died three weeks after the second stage from tuberculous pneumonia in the lower lobe of the operated side.

There were four late deaths, all following completion of the thoracoplastic work from four weeks to three months:

1 from tuberculous meningitis
1 from extensive renal involvement
2 apparently from gradually overwhelming autotuberculinization

The last three were undertaken much against our desire. We were persuaded to give them what they felt to be their only chance. We feel

definitely that these desperate risks lead to much more harm than possible good. Under certain circumstances, however, it is very difficult to refuse them.

In 98 the sputum is negative; in 13 it is still positive; in 94 the cavities are closed; in 17 the closure is not complete.

In 32 we removed 11-rib sections
In 61 we removed 7-rib sections
In 5 we removed 6-rib sections
In 18 we removed 5-rib sections
In 4 we removed 4-rib sections

In 6-rib resections the scapula usually catches beneath the 7th rib. Instead of resecting the 7th rib with the resultant sacrifice of good lung, we follow Eloesser's habit of removing the inferior end of scapula. Free movement of the scapula is thus regained and at the same time even scapula pressure against the collapsed lung is accomplished.

No definite decision is made before operation as regards the number of ribs to be removed. We plan to carry on to cavity closure, not cavity wall approximation, but with minimal sacrifice of uninvolved lung. It is very firmly our opinion that, unless cavity walls are actually brought together, healing does not take place. Usually, even in a patient whose cavity has been reduced to a slit, the sputum, perhaps months negative, eventually again carries tubercle bacilli. By dividing, not crushing, the last intercostal nerve at the end of each stage, post operative pain due to collapse-pull upon this nerve is greatly reduced or eliminated.

We do not take an X-ray film until 12 days following a thoracoplastic stage, since, as Oechsli has shown, serum and oedema in the soft tissues often obscure the lung fields and cavity, easily leading one to the hazardous conclusion of cavity closure. Nor do we content ourselves with the ordinary X-ray film taken for lung detail. The collapsed tissues effectually may hide a considerable cavity beneath. We follow the technique worked out by Oechsli at Olive View Sanatorium, which is similar to that used in visualizing the kidney; 75 K.V.P., 50 M.A., 30 in. dist. and $\frac{3}{4}$ to 1 sec., using the Potter-Bucky diaphragm. A very hard film is thus taken, often at two or three angles following this method. All lung detail is lost and bone detail is good. If a cavity is present, it can almost always be recognized. When there is a question, stereofilms are taken, for often the third dimension is convincing for or against a remaining cavity. We do not allow ourselves to be greatly influenced by a negative sputum. It is the cavity or cavities that are important.

In this series we have done 12 secondary operations; that is, we have removed widely the regenerated ribs. We recently finished a thoracoplasty where two previous thoracoplasties had been done. Of these twelve, four still have recognizable cavities with positive sputum. The cavities are very small, narrow, and close to the mediastinum, but we do not feel safe to allow them to be discharged until closure is assured. In two of these, we are following the Caspar gauze-packing technique. In one we unroofed the cavity posteriorly and packed. The sputum is negative but a fistula persists. In the other we shall free the parietal pleura from the ribs and vertebral bodies to obtain obliteration with packing by counterpressure against the anterior regenerated ribs.

At Olive View Sanatorium, where many of this series were done, we have 5 thoracoplastic patients with cavities yet discernible, including the one just mentioned. It is our great desire to eventually close these. There would seem to be no question that the time is very near when a medical team experienced in chest medicine and surgery can practically promise a patient who is a suitable operative risk that, barring complications, his cavities can be closed and his sputum rendered tubercle-bacilli free, provided he is willing to undergo the operative procedures that seem advisable to accomplish closure.

In large apical cavities reaching to the 7th rib posteriorly, it is not uncommonly true that a seven-rib operation, as described above, even with transverse processes and costal cartilage resection of the upper four, may still leave a narrow cavity close to the mediastinum. If the lower lobe of the lung is good, we feel it much more worth while to the patient to suffer a possible secondary thoracoplasty of these same 7 regenerated ribs than to sacrifice a considerable part of the good lung below. We believe that the primary extensive resection above with its marked collapse of inflamed lung produces sufficient irritation to the contiguous mediastinal structures to very greatly stiffen them, so that, in case a secondary thoracoplasty becomes necessary, this mesial wall of the cavity remains firmly fixed, and the probability of complete closure of the remaining cavity is much increased. Lung sacrifice has then been minimal.

In this series 12 patients suffered haemoptysis in varying amounts from time to time before operation. Only one bled after collapse,—the one who died of tuberculous meningitis.

Six had very marked paradoxical breathing. All but one of these obtained cavity closure and negative sputum.

Five had contralateral spread of the disease, but without additional

cavity formation. In two the greatly reduced original cavities are still apparent. In two the sputum is still positive.

In 12 cases a considerable therapeutic pneumothorax existed below, but owing to extensive adherence above, cavity closure had not been obtained. The X-ray films suggested that an extensive apical rib resection would collapse these cavities. The pneumothorax below could then be continued with a good expectancy for a cure. In application this procedure proved unsuccessful with us. In one case, even with an apparently satisfactory collapse above, the patient seemed worse than before operation, and now has considerable involvement on the opposite side. A second case developed a secondarily infected tuberculous empyema, and required an extensive 11-rib thoracoplasty to obliterate the pleural space following external drainage. A third had a marked shift of the upper third of the lung toward the mediastinum without complete cavity closure. In all the others, we have graduated our thoracoplasty according to the lung involvement existing before the pneumothorax, allowing the remaining uninvolved portion of the lung to reëxpand. In these last, the results have not differed from the series in general. We purpose to follow this latter plan hereafter. If an extensive upper lysis must be done to obtain cavity obliteration, pneumothorax is definitely stopped and sufficient thoracoplastic release is brought about to insure a collapse of all desired areas. Air aspiration to a -30 is done the day before each thoracoplastic stage, and at once after each stage.

In a number of patients we have measured the vital capacity before and after thoracoplastic collapse. Careful evaluation of such figures require much time and must be excluded from this paper. It should be mentioned, however, that, if before operation the vital capacity is below 2,000, one should reckon by auscultation and examination of X-ray films the probable percentage loss of functioning lung that would occur following the proposed rib removals. One must bear in mind also that marked paradoxical respiratory movement that often develops at once following an extensive upper-lobe thoracoplasty may temporarily greatly reduce the vital capacity, even though there actually has been little or no functioning lung collapse.

We have done, on the other hand, very extensive upper seven rib resections on patients whose vital capacity before operation was 850–800, and in one case 700 cc., without untoward results, since in these cases we were convinced that the lung portions to be collapsed were not contributing measurably to respiration. The ribs removed at each stage were few and

paradoxical motion little. In these patients there was practically no reduction in vital capacity when measured several weeks following the operations. Vital-capacity measurements in thoracoplastic patients are of definite value, particularly now when the trend is toward minimal lung sacrifice. The interpretations, however, and proper evaluation are often very difficult.

SUMMARY

We feel that the outstanding advances that have been generally made during the past three years in the thoracoplastic treatment of the patient suffering from pulmonary tuberculosis are these:

1. The gradation of rib resection both in length and number to fit the patient's condition, age and the character and extent of his pulmonary involvement.

2. The minimal sacrifice of uninvolved or healed lung, even though by so doing a secondary series of stages may be necessary.

3. The treatment of the periosteum with formalin or by some other method that will greatly retard bone regeneration, thus permitting us to extend the period between stages until definite recovery from the previous stage has occurred. In this way, not only has the mortality been reduced, but a vast number of patients previously excluded on account of age or poor general condition have become operable and their tuberculosis arrested.

4. It is being definitely recognized that the primary and all-important object of the surgical collapse of the chest is not to obtain relaxation or even approximation of cavity-walls, but rather cavity obliteration, for, unless the walls are actually in contact, it is very doubtful if actual scar-tissue healing will occur.

PHRENICECTOMY IN CLOSING PULMONARY CAVITIES AND END-RESULTS

OREN A. BEATTY[1]

This study has been made in an effort to evaluate end-results in tuberculous patients who have been treated by means of phrenicectomy in the Waverley Hills Sanatorium. The end-results are based chiefly on whether tuberculous cavities have or have not been closed following the operation; and it will be our endeavor to draw some conclusions as to the value of phrenicectomy as a form of treatment with particular reference to the type of case in which it is indicated.

For many months following the introduction of the phrenic-nerve operation as a major form of therapy in this institution it was done almost routinely as the operation of choice in cases in which surgery was indicated. If this procedure failed artificial pneumothorax was resorted to. Since that time, however, cases have been selected for this operation from the standpoint of its indications, and undoubtedly much more favorable results can be obtained when cases are selected in this manner. This can be readily seen when we analyze table 1 and take in consideration the 70 cases in which successful closure of cavities occurred. Centrally located, thin-walled cavities, less than one inch in diameter and surrounded by contractile lung tissue, respond favorably to phrenicectomy and in the absence of rapidly advancing acute tuberculosis this operation should be the procedure of choice. If under these conditions phrenicectomy fails artificial pneumothorax should then be considered.

Three hundred and fifty-one patients have been included in this series, of which 312 were white ranging in age from 14 to 64 years, and 39 were colored from 17 to 54 years. In the white group the first operation was done June 7, 1927, and the last operation was done December 3, 1931. In the colored group the first operation was done November 13, 1928 and the last operation March 19, 1932. The operations done since the above dates have not been included in this study. Therefore this is a study of a group of white patients who have had the operation $2\frac{1}{2}$ to 7 years, and a group of colored patients who have had it from $2\frac{1}{4}$ to $5\frac{1}{2}$

[1] Waverley Hills Sanatorium, Waverley Hills, Kentucky.

TABLE 1

Results in the series of white patients who had phrenicectomy

	NUMBER OF CASES	FAR ADVANCED	MODERATELY ADVANCED	MINIMAL	BRONCHIECTASIS	AVERAGE SIZE OF CAVITIES FOR GROUP	THICK WALLED CAVITIES	THIN WALLED CAVITIES	WORKING	APPARENTLY WELL	IMPROVED	UNIMPROVED	NO RECORD	IN SANATORIUM	DEAD
						cm.									
Cases in which cavities were closed following phrenicectomy alone	70	36	34			2.4	24	46	30	1	11	8	4	14	2
Per cent	22.7	51.4	48.6				34.3	65.7	42.9	1.4	15.7	11.4	5.7	20	2.9
Cases in which cavities were not closed following phrenicectomy	242	172	63	2	5	2.95	150	62	46	11	23	15	17	42	88
Per cent	77.3	71	26	0.9	2.1		62	38	19.0	4.5	9.5	6.2	7.0	17.4	36.4
Total	312	208	97	2	5		174	108	76	12	34	23	21	56	90
Per cent	100%	66.7	31.1	0.6	1.6				24.4	3.8	10.9	7.3	6.8	18	28.8

years. The end-results after this time should be rather indicative of the value of phrenicectomy.

The patients of both white and colored series were arbitrarily divided into two groups. One group in which phrenicectomy closed tuberculous cavities within one year was called the successful group; and one group in which phrenicectomy did not close the cavities within one year or did close the cavities, but with other surgical aids, was called the unsuccessful group, that is, unsuccessful in that phrenicectomy could not produce the desired effect. The maximum effects of the operation on the cavity should be obtained within six months after operation and certainly within one year as an outside limit. This is the reason for taking one year as the time limit. The closure of cavities was taken as the criterion of a successful operation, but of course this does not mean that treatment will be successful. The study of a group of patients who obtained closure of cavities after phrenicectomy and a group of patients who did not should be very valuable.

These patients were also studied as to classification of disease, location, type and size of cavity, sputum and as to status at the present time. In fact they were studied from many viewpoints, but to avoid the monotony of great detail only that which is pertinent to the subject is presented.

Part 1. White Patients

This series of 312 white patients ranging in age from 14 to 64 years was divided into two groups as stated above, and for the purpose of simplifying the study of end-results. One group consisted of those patients who had closure of their cavity or cavities within one year after phrenicectomy and the other group consisted of those patients who did not get closure of their cavities within one year or if closure took place was due to pneumothorax or some other surgical procedure and could not be credited to phrenicectomy.

(See table 1.) In the successful group there are 70 cases, which is 22.7 per cent of the white patients. Twenty-two and seven-tenths per cent of these patients had closure of their cavities within one year after phrenicectomy alone. The remainder had to have some other surgical procedure to aid closure or else they did not have closure. Thirty of the first group are working, one is apparently well, and eleven are improved. This makes 60 per cent who had favorable end-results from phrenicectomy alone. There are 8 unimproved, 4 with no record, 2 dead and 14

still in the sanatorium. This gives 40 per cent with unfavorable end-results. In the whole series of patients there are 76 working, 12 apparently well and 34 improved. This gives 39.1 per cent favorable results. Twenty-three are unimproved, 21 without record, 90 dead, and 56 in the sanatorium. This gives 60.9 per cent unfavorable end-results in the white patients. This shows a high percentage of unfavorable results regardless of the form of treatment, but these cases represent many that were done not as a form of treatment but for symptomatic relief. Two hundred and nine of these 312 cases were far-advanced and many had bilateral disease and many were recognized as eventually terminal cases. Seventy-one per cent of the unsuccessful group had far-advanced disease. The average size of the cavities in this group was 2.95 cm. Sixty-two per cent of the cavities had thick walls.

Table 1 is presented as it is in order to avoid much detail, but, since the second group of patients in this table represents such a varied lot, some explanation should be made, so that the reader may make deductions or calculations if he so desires. There were 30 cases without cavities included in the unsuccessful group. Of these, 9 were pneumothorax cases, 5 bronchiectasis, and the remainder of course tuberculous but without cavities. Twelve are working, one is apparently well, 5 are improved, 2 are unimproved, 4 have no record, 2 are in the sanatorium and 4 are dead. These cases without cavities represent a fairly good percentage of the number working in that group. Also, there were 6 cases of bilateral phrenicectomy all of which were in far-advanced disease. The results in these 6 cases show 1 improved, 2 in the sanatorium and 3 dead. Bilateral phrenicectomy was not successful in this small number of patients.

It may be mentioned here that, in the group of 70 cases that had successful closure of cavities following phrenicectomy, 11.4 per cent had subsequent surgical procedures, and that, in the group of 242 cases that did not have closure of cavities following phrenicectomy, 47.1 per cent received other surgical treatment. Pneumothorax was the most frequent procedure used after phrenicectomy. The patients who received additional surgical treatment furnished many of the favorable results in the second group of table 1.

The group in which phrenicectomy was successful in closing cavities may be called a selected group. This group contains 70 cases, 38 of which had right phrenicectomy and 32 left phrenicectomy. There were 36 far-advanced and 34 moderately advanced cases. The average size

of cavities was 2.4 cm. Twenty-four cavities, or 34.3 per cent, had thick walls, whereas 46, or 65.7 per cent, had thin walls. Sixty-one cavities, or 87.1 per cent, were not subpleural, and 9, or 12.9 per cent, were subpleural. Seventy-nine and seven-tenths per cent of them were in the upper third, 17.6 per cent in the middle third and 2.7 per cent in the lower third. Considering these patients as a group of 70 selected cases, then 60 per cent obtained favorable end-results from phrenicectomy alone. Forty per cent had unfavorable results, of which number there is no record of four. At discharge there were 16 patients who had positive sputum. At present, of this 16, there are one working, three improved, three unimproved, eight in sanatorium and one dead. This shows that 42.8 per cent of the unfavorable results was in the small group of patients who had positive sputum on discharge.

For the whole series of white patients there were 154 right-sided cases and 164 left-sided cases. More operations were done on the left side, but apparently for this series the right side was favored in results. In the same series the location of the cavities in the upper, middle and lower thirds was 72, 26.1 and 1.9 per cent, respectively. In comparing the locations of the cavities in the successful group with those in the unsuccessful group it seems that no particular location is favored by results. It does show the big majority of cavities in the upper third.

In studying the type of wall a cavity has and its relationship to closure we find that 42.6 per cent of the thin-walled cavities close following phrenicectomy, and 13.8 per cent of the thick-walled cavities. In the moderately advanced cases of the successful group, 73.5 per cent had thin-walled cavities and 26.5 per cent thick-walled cavities. In the far-advanced cases 61.1 per cent had thin-walled cavities, and 38.9 per cent thick-walled cavities. This shows that the thin-walled cavities were more favorably influenced by phrenicectomy in either moderately or far advanced diseases than were the thick-walled cavities. The average time of closure for the group was 159 days following operation. It is interesting to know as a comparison that in the colored patients the cavities closed 157 days following operation.

Part 2. Colored Patients

This is a review of 39 cases of colored patients who have had the phrenicectomy operation. The time since the operation varies from $2\frac{1}{4}$ to $5\frac{1}{2}$ years. The age of the patients ranged from 17 to 54 years. The object of the study is to evaluate the operation in the colored. Of

course, 39 patients are not a sufficient number from which to draw any final conclusions but are sufficient to make an interesting study. These cases were studied as to location and size of cavities, thickness of walls of the cavities, amount of surrounding fibrosis, classification of lesion, sputum, and the relation of any other surgical procedure to the operation.

(See table 2.) The cases here were divided into two groups according to results as in the white series. In the successful group which may be called the selected group, 5 patients, or 12.8 per cent, of all the colored

TABLE 2

Results in the series of colored patients who had phrenicectomy

	NUMBER OF CASES	FAR ADVANCED	MODERATELY ADVANCED	MINIMAL	AVERAGE SIZE OF CAVITIES	WORKING	APPARENTLY WELL	IMPROVED	UNIMPROVED	NO RECORD	IN SANATORIUM	DEAD
					cm.							
Cases in which cavities were closed following phrenicectomy alone	5	5			2.14	2	1	1	1			
Per cent	12.8	100				40	20	20	20			
Cases in which cavities were not closed following phrenicectomy	34	31	3		2.8	6		3	1	2	3	19
Per cent	87.2	91.2	8.8			17.6		8.8	2.9	5.9	8.8	56
Total	39	36	3			8	1	4	2	2	3	19
Per cent	100%	92.3	7.7			20.5	2.5	10.2	5.1	5.1	7.7	48.7

patients obtained closure of cavities within one year after phrenicectomy alone. In this group there are 2 working, 1 apparently well, 1 improved, and 1 unimproved. This makes 80 per cent favorable results for this group and 20 per cent unfavorable results. For the whole series there are 8 patients working, 1 apparently well, 4 improved, 2 unimproved, 2 no record, 3 in sanatorium and 19 dead. This gives 33.2 per cent favorable results and 66.8 per cent unfavorable results.

But, considering this successful group as a whole, the results are highly favorable. Eighty per cent showed favorable and 20 per cent unfavorable

end-results. This shows better results than for the same group of white patients, but, of course, figures from a group of patients as small as this are less accurate than in the larger series of white patients. Also remember that 22.7 per cent of the white patients obtained closure of cavities from phrenicectomy alone against 12.8 per cent in the colored. It may be mentioned here that in the second group of table 2 were two patients who did not have cavities, of whom one is dead and one is improved. In the first group of table 2 no subsequent operative procedures had to be used, whereas, in the second group of table 2, 35.3 per cent of the patients had other operative procedures. This of course increased the favorable results for this group. Pneumothorax was the most frequent procedure used.

The lungs arbitrarily were divided into upper, middle and lower thirds. Twenty-eight, 8, and 2 cavities were respectively in the upper, middle and lower thirds for the whole series of patients. This is 73.7, 21 and 5.3 per cent, respectively. In the successful group, 5 and 2 cavities were in the upper and middle thirds respectively. None were in the lower third. This is 71.4 and 28.6 per cent, respectively, for the upper and middle thirds. This shows the middle third somewhat favored for closure in this colored group.

Thirty-six cases on admission were far advanced. Three on admission were moderately advanced. All of the 5 successful cases were on admission far advanced. All of the successful cases had on discharge or developed during residence following phrenicectomy a negative sputum. Only one other patient was discharged with a negative sputum and this patient did not have a positive sputum on admission and during residence. Seven other patients of the whole group are running a negative sputum from a few months to several months duration.

Of the 5 successful cases four had thin-walled cavities and a moderate amount of fibrosis with nō or a moderate amount of infiltration on the opposite side. None of these thin-walled cavities were subpleural. One of these cases had two cavities. There were two thick-walled cavities with much fibrosis surrounding. These two cavities were in one patient who had unilateral disease. The average size of the cavities in the successful group was 2.14 cm. The average size in the unsuccessful group was 2.8 cm. In other words the cavities in the successful group averaged less than one inch in diameter and in the unsuccessful group more than one inch in diameter.

For the whole series there were 23 right and 16 left phrenicectomies. All of the patients in the successful group had right phrenicectomy. There were no cases of bilateral phrenicectomy.

If conclusions could be drawn from such a small number of patients one would have to say that, if phrenicectomy in the colored is to be fairly successful, moderately advanced or less extensive lesions with cavities less than one inch in diameter, thin-walled, not so much surrounding fibrosis and with surrounding lung tissue, would have to be selected. Certainly, anything more extensive than the above should have an initial trial of pneumothorax. Phrenicectomy in this group of far-advanced cases has not been successful; and if the colored patients of moderately advanced extent of disease and with other favorable indications for phrenicectomy do not respond well to the operation then pneumothorax should be the initial procedure in all suitable cases. It is questionable whether phrenicectomy in moderately advanced cases would improve results enough to justify giving it preference over pneumothorax in otherwise suitable cases.

DISCUSSION

Results in this series of patients were unfavorable, 60.9 per cent in the white and 66.8 per cent in the colored. All ages and types of disease and all ages and types of patients were represented. In many cases in which phrenicectomy was unsuccessful there was extensive disease, bilateral, oftentimes with multilocular cavitation, and much fibrosis. There was variation of this same general picture. This may account for the unfavorable results to some extent. On the other hand in the successful group there were found more patients conforming to the same general picture of less extensive disease, with thin-walled cavities and elastic lung tissue surrounding the cavities. This group, considered as a whole, showed highly favorable results, 60 per cent in the white and 80 per cent in the colored. This definitely indicates that cases for phrenicectomy should be carefully selected after clinical and roentgenological study. The indications for the different surgical forms of treatment for tuberculosis are becoming more definite and that form of treatment considered adequate for a certain type of disease should be the first tried. Ornstein, Ulmar and Dittler (1) emphasize that the type of tuberculosis should determine the choice of treatment.

The results in the white series of patients somewhat agree with those reported by Bronfin and Chernyk (2). O'Brien (3), in reporting 500

cases, reported only the influence of phrenicectomy upon the cavity. The immediate results in this series of cases no doubt would approximate O'Brien's as far as the influence of phrenicectomy on the cavity is concerned, but it would be interesting to know what the end-results of his 500 cases would show now. Werner and O'Brien (4) reported 100 cases, in which 23.9 per cent of the cavities closed following phrenicectomy. This agrees favorably with 22.7 per cent in this group. They did not report end-results.

SUMMARY AND CONCLUSIONS

1. Results in 351 phrenicectomies, 2¼ to 7 years following operation, were not highly favorable in all ages and types of disease and in all ages and types of patients.
2. Results in a selected group were very favorable.
3. The best results were obtained in those cases having moderately advanced disease with cavities less than one inch in diameter, thin-walled, and with contractile lung tissue surrounding them.
4. End-results justify phrenicectomy in only a selected group.
5. The location of a cavity in the upper, middle, or lower third did not favor its closure in the white patients. In the small group of colored patients the cavities in the middle third were favored in results.
6. The right lung was favored to a small degree by results in both colored and white for this series.
7. Bilateral phrenicectomy did not give favorable results in six cases.
8. Results in the colored race were analogous to those in the white race but to a less favorable extent.

I wish to take this occasion to express my thanks and appreciation for the very helpful suggestions in the writing of this paper made by Dr. Lawrason Brown, Saranac Lake, N. Y. and Dr. Benjamin L. Brock, Waverley Hills, Ky.

BIBLIOGRAPHY

(1) Ornstein, G. G., Ulmar, D., and Dittler, E. L.: A clinical classification of pulmonary tuberculosis, Amer. Rev. Tuberc., 1931, xxiii, 248.
(2) Bronfin, I. D., and Chernyk, M.: The value and limitations of phrenicectomy in advanced pulmonary tuberculosis, Ibid., 1932, xxvi, 689.
(3) O'Brien, E. J.: Phrenic nerve operations in pulmonary tuberculosis, Jour. Am. Med. Ass., 1930, xcv, 650.
(4) Werner, W. I., and O'Brien, E. J.: The effect of phrenicectomy on pulmonary cavitation, Amer. Jour. Roentgenol., 1930, xxiv, 626.
(5) Nehil, L. W., and Alexander, J.: An estimate of the value of phrenic nerve interruption for phthisis based on 654 cases, Jour. Thorac. Surg., 1933, ii, 549.
(6) Mayer, E.: The cavity in the tuberculous, Jour. Am. Med. Ass., 1933, c, 1480.

CULTURAL CHARACTERISTICS OF THE R1 STRAIN OF TUBERCLE BACILLUS WITH PARTICULAR REFERENCE TO DISSOCIATION[1]

GERALD R. DOWD

Previous experience in the Saranac Laboratory has indicated that infection with the attenuated strain of tubercle bacillus, R1, will produce progressive tuberculosis in animals with coexisting silicosis. Among the possible explanations for this effect, the phenomenon of bacterial dissociation has been entertained (1). Before studying cultures obtained from animals with silicosis, however, it was deemed advisable to attempt to dissociate the stock culture of this organism and to determine whether differences in colony structure were associated with detectable variations in virulence for animals. The present communication will be confined to a description of the variations in colony structure, and the virulence of the bacilli composing the several forms.

The history of the R1 strain has been recently reviewed by Gardner (2). In this connection it suffices to state that it has been under artificial cultivation since 1891, that it is probably of human type, and that in normal guinea pigs it produces infectious lesions which caseate and later heal. Isolation from animal tissues is somewhat difficult. Once isolated, however, difficulty is not encountered in subsequent transplants.

CULTURAL CHARACTERISTICS

Solid medium: The stock culture grows readily on all the ordinary laboratory media containing glycerol. Grown in the routine manner, in tubes containing glycerolated agar, Dorset's or Petroff's egg medium, it exhibits the usual dry granular appearance of most human and bovine bacilli, but, as a rule, it tends to be chromogenic, even in young cultures. Isolated colonies on solid media, especially on Petroff's egg medium, present certain characteristic peculiarities.

Fluid medium: The growth on fluid media more closely resembles the human than the bovine type. On glycerolated broth the color is dis-

[1] From the Saranac Laboratory for the Study of Tuberculosis of the Edward L. Trudeau Foundation, Saranac Lake, New York.

tinctive, being a deep cream in the heavier growth. There is a tendency to develop dense, usually chromogenic, "island-like" areas, where the growth is heaped up and its lower surface extends beneath the surface of the medium. In some instances the growth is continuous, appearing lattice-like. It is difficult to remove small portions with a loop because the growth is coherent, and fragments are not easily broken away.

Surrounding the heavier masses there is almost always a thin, veil-like growth, whose consistence varies from a scum-like film to a finely granular, and frequently a smoothly wrinkled or corrugated formation. This veil-like growth is never chromogenic and may be easily broken and removed with a loop. Variations are, of course, to be expected. After 6 to 8 weeks the growth becomes profuse and covers the entire surface of the medium, often creeping up the sides of the bottles. These older cultures usually become moist and tend to sink beneath the surface of the fluid. The old cultures yield a highly potent tuberculin.

Cultures on Proskauer and Beck's and similar synthetic media resemble those on glycerolated broth.

The hydrogen-ion concentration of the medium between pH 6.6 and 7.4, the customary range for tubercle-bacillus cultures, does not affect the type of growth materially. There may be some slight increase in the initial lag period on transferring the organism to a medium of altered reaction, but it readily accommodates itself to the new environment and grows luxuriantly in subsequent transplants.

MORPHOLOGY AND STAINING REACTION

The R1 bacillus presents nothing distinctive morphologically. It is a slender pleomorphic rod, 2 to 5 micra in length. It is strongly acid-fast, and, when stained by the Gram method, it retains the gentian violet.

USUAL ANIMAL VIRULENCE

At the present time, the R1 strain is not pathogenic for rabbits. Repeated doses of 10 mgm., administered intravenously, have failed to produce apparent disease.

For guinea pigs it is only slightly pathogenic. Irrespective of the mode of infection the type of disease is the same. Animals infected subcutaneously in the groin develop enlargement with foci in the superficial inguinal lymph nodes. The disease may or may not extend to the deep inguinal, parailiac, hepatic, and tracheobronchial lymph nodes.

Occasionally, the spleen may show some chronic disease, but, as a rule, the viscera are not involved. These lesions tend to heal after some months, leaving only foci of fibrosis.

When produced by inhalation, the infection manifests itself by the formation of small, 1- to 2-mm., caseous, subpleural tubercles and enlarged, caseous, tracheobronchial lymph nodes. The pulmonary foci generally retrogress and completely resolve after 10 to 18 months (Gardner (3)).

Occasionally, chronic disease with more extensive involvement of both the lymph nodes and the viscera has been encountered (4). Such an outcome is unusual and is not regarded as typical of R1 infections. When it occurs, undefined variations in the resistance of individual animals may account for it. This seems to be the case because, on subinoculation of such tissues, there is no evidence of unusual virulence of the organisms. In a few instances, generalized tuberculosis of an acute miliary type has occurred in this laboratory in guinea pigs inoculated with the R1 bacillus. As pointed out in previous communications (4) (5) we have regarded such cases as due to accidental superinfection rather than to the R1 inoculation; for when the tissues are injected into other animals, a virulent tubercle bacillus, often of bovine type, has been recovered.

TECHNIQUE OF DISSOCIATION

The technique employed conformed closely to that described by Petroff (6) for dissociation of tubercle-bacillus cultures, but certain minor modifications have been found necessary to satisfy the somewhat peculiar requirements of the R1 strain. Experience has shown that it is necessary to inoculate plates with a much heavier suspension of R1 organisms than Petroff recommends for other strains of tubercle bacilli. Consequently, only one layer of paper (Whatman No. 5) is used in filtration, and the resulting filtrate is not diluted but is seeded directly. We have substituted Proskauer and Beck's synthetic medium pH 7.4 to 7.6 for physiological saline solution in the preparation of the suspension, as it has been suggested that the latter may be unfavorable to the development of the virulent or S type of colony.

With a sterile platinum-iridium wire spade (gauge 18) a small portion of culture is aseptically removed to a "Wassermann" test-tube containing 5 cc. of Proskauer and Beck's medium. The culture is deposited on the side of the tube above the fluid level and triturated with the wire

against the glass, gradually adding fluid from below until the process is completed.

The suspension is carefully mixed with a capillary pipette provided with a rubber nipple. It is then filtered through a single layer of Whatman No. 5 filter-paper folded into a small funnel made from 22-mm. glass tubing, as recommended by Petroff (6). The filtrate is finally refiltered through the same paper.

With a capillary pipette, from 3 to 7 drops of the final filtrate are seeded on the surface of Petroff's gentian-violet-glycerol-egg plates, both with and without 0.25 per cent sodium taurocholate. In practice, three of each type of petri plates have been inoculated. The addition of 6 to 8 drops of sterile Proskauer and Beck's medium to the surface facilitates the spreading of the inoculum.

The seeded plates are incubated over night at 37.5° C., with the surface of the medium upward to permit evaporation of any excess of water. They are then sealed with Petroff's rubber bands (6) at incubator temperature and inverted so that the surface of the medium faces downward. Every four or five days the bands must be momentarily snapped off to insure proper aeration of the cultures; but, as Petroff states, it is essential that this also be done at incubator temperature, for otherwise contaminations will certainly occur.

Colonies generally appear in three to four weeks, but should be allowed to grow for six or seven weeks. They will, by that time, have matured sufficiently to assume a more definite form for study and subculturing.

For this study 1 to 3 drops of an unfiltered suspension prepared from the veil-like growth of a 12-day R1 culture growing on glycerolated veal-broth, pH 6.8, were seeded on 6 plates. Filtration was omitted in this initial generation to ensure an adequate growth on the new medium. From this unfiltered suspension, growth on the plain medium appeared in 10 to 14 days, but on taurocholate medium it required a few days longer. After five weeks numerous isolated colonies had developed on both media. They were of one type: namely, a rough, uneven, dull-surfaced, burr-like colony rising abruptly from the medium (figure 4).

The colonies were chromogenic and grew more vigorously on the plain medium, while those on the medium containing ox-bile salt appeared white and wax-like. The wax-like appearance is characteristic of all colonies on taurocholate media and is due presumably to the increased moisture retained by the presence of the salt. No pigment is produced

on the latter medium except in old cultures, and then it is very slight and is confined to the centre of the colony; whereas on plain medium, even in young cultures, pigmentation may be marked in all portions of the growth.

When colonies were about six weeks old, they were subcultured by the method described.

Typical R and S characteristics were not present in the first few generations. Repeated subculturing has resulted in the development of at least 5 more or less distinct types of colonies. The characteristics of these colonies, including the virulence of the bacilli composing them have been studied.

Fig. 1. Dissociated "R" type colony cultivated on Petroff's gentian-violet-egg medium containing 0.25 per cent sodium taurocholate. × 6

Fig. 2. Dissociated "S" type colony cultivated on Petroff's gentian-violet-egg medium containing 0.25 per cent sodium taurocholate. × 6

Fig. 3. Dissociated "S" type colony cultivated on Petroff's gentian-violet-egg (plain) medium. × 6

Fig. 4. Intermediate "Burr" type colony cultivated on Petroff's gentian-violet-egg (plain) medium. × 7½

Fig. 5. Intermediate type colony showing "R" (center) and "S" (periphery) characteristics, cultivated on Petroff's gentian-violet-egg medium containing 0.25 per cent sodium taurocholate. × 6

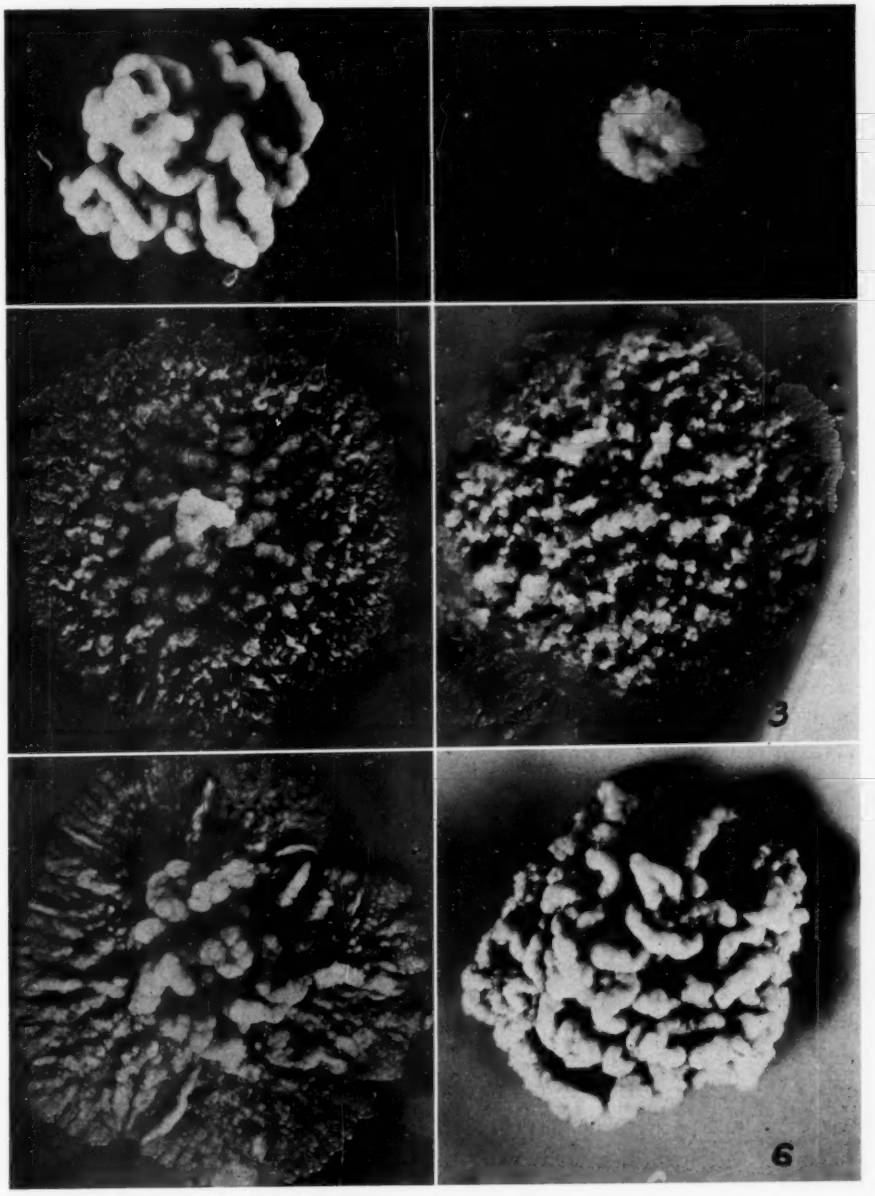
Fig. 6. Intermediate "R" type colony showing secondary papillae ("S" characteristics) growing on the convolutions. Cultivated on Petroff's gentian-violet-egg (plain) medium. × 6

TYPICAL R AND S FORMS OF COLONIES

Figures 1 and 2 illustrate the appearance of the two types which conform to the accepted colony structure designated respectively as R and S.[2] Rarely both types have been seen on the same plate but usually several plates of one seeding must be searched before typical colonies can be discovered.

The R form (figure 1), grown on Petroff's taurocholate medium, is composed of smooth, glistening, irregularly entwined folds, white and wax-like, resembling the convolutions of the cerebrum. The margins of this colony are abrupt and there is no penetration into the substance of

[2] The symbols *R* and *S* in this study should not be confused with the terminology of workers with other bacteria who employ them to designate "rough" and "smooth" colony appearance. We have used them as a matter of convenience rather than for their descriptive value, *R* designating the abrupt-periphery colonies which we assume to be avirulant, and *S* the colonies with a spreading periphery, presumably composed of virulent bacilli.



Figs. 1-6

the medium. It is never chromogenic. On the plain medium the pure R form is apt to be complicated by the development of secondary papillae on the convolutions and at the base of the colony. Such growths have been classified as intermediate types of colonies (figure 6), and are described below.

The S form (figure 2), grown on taurocholate medium, consists of a small, raised, compact centre, which is usually white, chromogenicity occurring only in rare instances in young cultures and then in very slight degree. The centre is surrounded by a white, finely granular zone, which tapers toward the periphery, becoming thin and veil-like at the margin. Its borders are ill-defined and firmly adherent to the medium. In occasional instances the raised central portion may be absent. All taurocholate colonies present a moist, glistening appearance.

The S form grows readily on plain medium. Its raised centre is invariably chromogenic, while the surrounding granular area often remains cream-colored, especially in young cultures. Uniform pigmentation frequently occurs. The granular zone is coarser on this medium than it is on the taurocholate, a feature which, combined with the pigmentation and the other appearances mentioned, readily identifies the source of the culture.

The raised central portion of the S type is frequently absent (figure 3), in which case the growth generally consists of only a raised granular zone which tapers outward, becoming more finely granular toward the periphery, sometimes graduating into a veil-like structure. Chromogenicity is almost invariably present, even in young cultures. The colonies appear dry and dull-surfaced.

INTERMEDIATE TYPES

There are more types of colonies which recur with sufficient constancy to require investigation. They are illustrated in figures 4, 5 and 6. We have referred to them as intermediate forms. The first (figure 4), we designate as a "burr." It is a small colony with a rough, uneven, stucco-like surface and an abrupt border. It is usually chromogenic on plain medium, but pigmentation is lacking on the taurocholate medium. This type almost invariably occurs in initial cultures on solid media.

The second type (figure 5) appears to have both R and S characteristics. It has a large, raised, convoluted centre, resembling the R colony and a peripheral granular zone. The marginal veil of the typical S form is usually absent. On plain medium the centre is invariably

chromogenic, with or without pigment in the granular structure. On taurocholate medium the pigment is almost always absent, and, when it does occur, it is confined to the centre and is very slight in amount. Colonies from the two media are readily differentiated. At times the convoluted structure of the central portion is poorly developed, and the growth may be solid and compact.

The third type (figure 6) more closely approximates the R form, with small out-growths having S characteristics. It somewhat resembles the previous type, but both the convolutions of the central portion and the borders of the colony are studded with small, finely granular papillae, which have been assumed to represent S characteristics. Chromogenicity in this type of colony never occurs on taurocholate medium and is only present to a limited degree on plain medium.

INSTABILITY OF THE TYPES OF COLONIES

None of the types is stable in successive generations on artificial media, and it has not been possible to stabilize them by any of the accepted methods regularly employed, such as the use of alkaline and acid media, or the addition of normal unheated sera to such media.

Variations would most naturally be expected to appear in the intermediate forms (figures 4, 5 & 6), since we assume both R and S characteristics to be present in the bacilli composing them. But, on the other hand, the colonies illustrated in figures 1 and 2, which we consider to be actual dissociates and which conform to the accepted colony structure, designated as R and S, also invariably fail to reproduce in kind on subculturing. Both the R and S colonies (figures 1 & 2), particularly the R form, make their appearance with regular frequency after the fifth generation and in occasional instances they may be encountered on the same plate. The S form sometimes appears as early as the third or fourth generation. Further subculturing through fourteen generations has failed to stabilize the character of colony formation. When, according to our custom, 6 plates are seeded with a suspension from a single colony, the resulting colonies which develop resemble neither the parent colony nor each other in the majority of instances. Dissociated forms have appeared with no apparent relationship to the type of colony from which they were derived.

If the several colony forms had developed from the same suspension on each of a series of plates, it would be easy to assume that complete dissociation had not been attained, and that both R and S bacilli were

present in the suspension used. But we are unable to explain the occurrence of the variations just noted, when the conditions of cultivation were as nearly identical as possible.

A STUDY OF THE FLUID CULTURES

The experience of others (6)(7)(8)(9)(10) has shown that with some strains of tubercle bacilli the type of growth may be influenced by cultivation on fluid media of various hydrogen-ion concentrations. It has been assumed that the veil-like growth produced on fluid media by certain other strains of tubercle bacilli are S, or virulent, forms, and that the coarse portions represent R, or avirulent, forms. Furthermore, media of alkaline reaction (pH 7.6 to 7.8) are said to favor the development of S characteristics, while those having an acid reaction (pH 6.5 to 6.8) tend to produce R. Accordingly the several types of growth already described for the R1 strain were studied on fluid media.

Cultures were grown on glycerolated veal-broth, Long's synthetic, and Proskauer-Beck synthetic media, the latter being selected because of its buffered qualities. After adjusting the hydrogen-ion concentrations to pH 6.5 to 6.8 and pH 7.6 to 7.8, respectively, the media were sterilized in the usual way.

In addition, the effect of normal body fluids was investigated. These included unheated normal horse- and guinea-pig sera and whole blood from the guinea pig. These substances in 10 per cent proportions were added to the various fluid media just mentioned. After one or two transplantations, all the media supported a vigorous growth of the R1 bacillus, which attained its maximum growth in 14 to 16 days. Every two to three weeks transfers were made to the same type of fluid media and occasionally the growth was put on to egg plates.

After two years' experience, we have been unable to obtain results with the R1 strain comparable to those described for other strains of tubercle bacilli.

ANIMAL VIRULENCE TESTS

An extended series of animal inoculations has been made to test the virulence of the bacilli composing the various types of colonies described. Ninety animals were injected with measured doses of the 5 types of colonies, respectively, but consistent differences in virulence could not be demonstrated.

DISCUSSION

This study has been made to demonstrate whether by continued culture of an attenuated strain of tubercle bacillus, two types of colonies would appear, analogous to those in the studies of the pneumococcus and other organisms, in which one colony is composed of virulent and the other of avirulent forms.

In addition, such a study of the particular strain, R1, was necessary as a control to further work on the bacteriological aspects of tuberculosis in experimental silicosis, in which this organism has been extensively employed. This work will be reported in still another paper.

The R1 strain of tubercle bacillus is peculiar in many respects. Gardner (2) has recently presented data indicating that it was originally of human type. However, at the time this study was started, the possibility of bovine origin was entertained. Accordingly, Petroff's gentian-violet-egg medium, with and without sodium taurocholate, was used because Petroff (6) has pointed out that bovine strains would dissociate more readily under the influence of the ox-bile salt, which favors the development of R forms. On the other hand, a medium without this substance is assumed by the same author to favor the S form of colonies.

Since the R1 strain is now thought to be a human type it might seem that the methods of culture employed were not suitable for the purpose in hand. However, it has been noted throughout this work that the sodium taurocholate does have a definite influence on the general appearance and structure of not only the R- and S-type colonies, but also the intermediate ones, a result which has not been obtained with other human strains. These effects include, lack of chromogenicity; increased moisture, and a consequently smooth, glistening, almost wax-like appearance of the colonies, together with a tendency to produce a finer, granular structure in the S form, and a well-defined, smooth-surfaced, cerebrum-like folding of the R colony.

Sodium taurocholate does not influence the stability of the R colony and the S form is not stable on egg medium in which this substance is lacking. Perhaps the R1 strain presents individual characteristics of instability. We have been unable to obtain results comparable to those reported by Reed (9) and others working with different strains of acid-fast organisms. Types of growth on solid and fluid media have been markedly inconsistent in failing to reproduce in kind.

We have found that when bacilli are transferred from stock cultures

and carried for four to fourteen successive generations on solid media, 5 distinct types of colonies will sporadically make their appearance. Slight variations in the intermediate types of colonies may occur, but they are not significant. That two distinctly different types of colonies have appeared on the same plate is probably definite evidence of dissociation as far as colony structure is concerned. It must be admitted, however, that such occurrences have been rather infrequent.

CONCLUSIONS

1. In our attempt to dissociate the R1 human strain of tubercle bacillus, into virulent and avirulent mutants, we have been able to demonstrate regularly five types of colonies.

2. Two of these types of colonies we consider actual dissociates as far as structure and appearance are concerned.

3. We have been unable to stabilize these two types so that they will reproduce in kind.

4. Attempts to stabilize different types of growth developing on fluid media have likewise been unsuccessful.

5. Hydrogen-ion concentrations, varying between 6.5 and 7.8, have failed to influence the type of growths or the virulence of the bacilli.

6. We have not observed a correlation between thin, veil-like and rough, heaped-up types of growth on fluid media and R and S types of colonies on solid media.

7. Animal inoculation has demonstrated no correlation between virulence and colony structure.

BIBLIOGRAPHY

(1) GARDNER, L. U.: Studies on experimental pneumonokoniosis. V. The reactivation of healing primary tubercles in the lung by inhalation of quartz, granite and carborundum dusts, Amer. Rev. Tuberc., 1929, xx, 833 & 875.

(2) GARDNER, L. U.: The R1 strain of tubercle bacillus. A record of forty years experience with an attenuated organism, Tubercle, August, 1932.

(3) GARDNER, L. U.: Healing by resolution in experimental tuberculosis, Amer. Rev. Tuberc., 1933, vi, 163.

(4) CUMMINGS, D. E., AND DOWD, G. R.: Generalized tuberculosis in guinea pigs infected with the attenuated strain of tubercle bacillus, R1, Ibid., 1932, xxvi, 379.

(5) CUMMINGS, D. E.: The virulence of the attenuated strain of tubercle bacillus, R1, after serial passage through previously tuberculin-negative guinea pigs, Ibid., 1932, xxvi, 369.

(6) PETROFF, S. A., AND STEENKEN, W., JR.: Biological studies of the tubercle bacillus. 1. Instability of the organism—microbic dissociation, Jour. Exper. Med., 1930, li, 831.

(7) PETROFF, S. A., BRANCH, A., AND STEENKEN, W., JR.: A study of Bacillus Calmette-Guérin (*BCG*). 1. Biological characteristics, cultural dissociation and animal experimentation, Amer. Rev. Tuberc., 1929, xix, 9.

(8) SASANO, K. T., AND MEDLAR, E. M.: Studies of the Calmette-Guérin strain of tubercle bacillus (*BCG*). 1. The effect in vitro of environment on the virulence of *BCG*, Ibid., 1931, xxiii, 215.

(9) REED, G. B., AND RICE, C. E.: Studies in the variability of tubercle bacilli. 1. A rapid growing bovine type, Canadian Jour. Research, 1931, iv, 389.

(10) REED, G. B., AND RICE, C. E.: Studies in the variability of tubercle bacilli. 2. Correlation of colony structure, acid agglutination and virulence, Ibid., 1931, v, 111.

A BACTERIOLOGICAL STUDY OF ATTENUATED (R1) TUBERCLE BACILLI RECOVERED FROM SILICOTIC AND NORMAL GUINEA PIGS[1]

GERALD R. DOWD

Experimental evidence is still accumulating to substantiate previous observations that the inhalation of silica dust materially alters the course of tuberculous infection produced by the attenuated human tubercle bacillus, R1. In normal guinea pigs, inhalation infection with this organism results in the formation of tubercles beneath the pleura of the lung and associated involvement of the tracheobronchial lymph nodes. These foci progress to caseation and heal, apparently because the bacilli die. The majority of the pulmonary tubercles completely resolve and disappear but lymph-node lesions often become fibrous (1). Subcutaneous inoculation usually produces lesions confined to the lymphatic system although involvement of the spleen may occur when the dosage is large (2). The presence of silica in the tissues alters the characteristic picture. As long as the lung harbors living R1 tubercle bacilli, the inhalation of quartz dust will cause these organisms to multiply continuously and produce chronic progressive tuberculosis (3). If infection with the attenuated tubercle bacilli is superimposed upon a preëstablished silicosis there ensues an acute tuberculosis with fatal termination in 2 to 6 months (4). In so far as observations have been made, this effect, with one exception, is specific for silica. The carbide of silicon (5), which is said by its manufacturers to contain no uncombined silica, acts in this respect quite like quartz. The inhalation of soft coal (6) marble (7) and gypsum (4) dusts do not appreciably affect the course of R1 tuberculous infection. The only silicate that has thus far been tested is asbestos, the silicate of magnesium (8). This substance is not particularly active in its effect upon the infectious process. In a few animals chronic progressive lesions were produced, but generally the tubercles tended to remain localized and healed with excessive amounts of fibrosis.

[1] From the Saranac Laboratory for the Study of Tuberculosis of The Edward L. Trudeau Foundation, Saranac Lake, New York.

All of these studies have been based on anatomical findings; bacteriological investigation has been limited to subinoculation of the lungs of a few guinea pigs with silicotuberculosis into other animals, and the culture of one or two of them, to determine whether accidental superinfection with virulent tubercle bacilli was occurring. No explanation for the apparently specific effect of silica dust in changing the course of R1 tuberculosis has been discovered. Among the possibilities to be considered is an alteration in the infecting organism. Petroff and Steenken's (9) work on dissociation of tubercle bacilli suggested the hypothesis that the presence of silica in the tissues might favor the development of an excess of "S" or virulent mutants (3). A preliminary study of a stock culture of this organism demonstrated that the application of their technique would produce colonies resembling those which these authors claimed to be characteristic of R and S mutants (10) for other strains of tubercle bacilli.

It was therefore decided to repeat one of the original experiments, in which guinea pigs were infected by the inhalation of R1 organisms and immediately exposed to daily inhalations of silica dust over a prolonged period. The organisms recovered from both dusted and nondusted control animals killed at intervals after infection were to be systematically studied by culture and by subinoculation into other guinea pigs. If virulent mutants should occur in significant numbers the change should be manifested by the type of colony developing on artificial media and by the extent and character of the disease produced in the subinoculated animals.

EXPERIMENTAL PROCEDURE

Forty guinea pigs were infected by the inhalation of R1 tubercle bacilli, using the same method previously employed (1). Each animal received 6 puffs from a de Vilbis "vaporizer" containing a water-clear suspension of tubercle bacilli, showing 10 to 15 isolated organisms per oil-immersion field. Twenty-five of these guinea pigs were then exposed in a dusting room for 8 hours daily, 6 days a week, to a high concentration of silica dust. The average light field counts in this room were somewhat over 4,000 million particles per cubic foot of air. In the same room were some of the animals which served as a basis for the paper on the reaction of normal guinea pigs to inhaled silica dust (11). The dust used in the experiment, known as "silica smoke," was exceedingly fine, over 90 per cent of the particles in the atmosphere being less than 10 micra in diameter and the majority of them less than 1.5 micra.

Chemical analysis showed a free silica content of 90.75 per cent, the balance being iron and aluminum. No petrographic investigation was made at the time the simple silicosis paper was reported, but a later analysis by Alden H. Emery of the U. S. Bureau of Mines demonstrated this dust to be composed of porous, cellular, cryptocrystalline quartz of the chalcedony type with 12 or 15 per cent of normal quartz fragments. Particles of the latter had sharp points and edges, while those of the cryptocrystalline material had rounded surfaces. No sericite was present.

The animals exposed to this dust, together with undusted but infected controls, were killed in groups at monthly intervals over a period of 15 months. For unexplained reasons the infection was unusually light. In most animals the lungs showed only 1 or 2 subpleural tubercles and, in some, killed during the first few months, the lungs showed no lesions but the disease was confined to the tracheobronchial lymph nodes. No spread of this infection occurred in any animal killed up to the 8th month, but in 2 dusted guinea pigs, killed on the 9th month, there were respectively 15 and 30 subpleural tubercles and these lesions showed a definite tendency to extend locally into the surrounding lung. However, evidence of progression of the infection ceased at this point and the tubercles observed in the 7 remaining guinea pigs, killed during the following 6 months, were even fewer in number and all manifested a tendency to heal by resolution or fibrosis. Characteristic silicotic nodules had developed by the 9th month, but they will be described elsewhere.

In the undusted infection-control group, only about 10 per cent of 15 animals showed anatomical evidence of tubercle although all of them reacted to an intracutaneous tuberculin test (in 2 cases the reaction was weak).

Because this first experiment had failed to reproduce the results obtained in preliminary observations, it was repeated. This time 50 guinea pigs were infected by inhalation of a dose approximately four times as large. The resulting infection developed satisfactorily. The half which were reserved as controls and the animals exposed to dust, which were killed early in the course of the exposure, all showed from 10 to 20 isolated subpleural pulmonary tubercles and an extensive involvement of the tracheobronchial lymph nodes. Eleven of the 13 dusted animals surviving to be killed between the 6th and the 15th month showed a spread of the infection under the stimulus of the inhaled quartz. The two exceptions were animals that developed epizoötic pneumonia. In the undusted control group the pulmonary tubercles began to heal

after the 4th month and by the 7th all traces of caseation had disappeared. Five control guinea pigs, killed after 15 months, showed only fibrous scars with foci of calcification in one case. Further details of the histopathology will be considered in another publication; this paper is restricted to the bacteriological findings.

TREATMENT OF TISSUES

The animals were killed with chloroform, the hair was thoroughly wet, and a median strip of skin was removed from the whole length of the ventral surface of the body. With fresh sterile instruments the rest of the skin was dissected away. The trachea was exposed and two loose ligatures were placed about it. The thorax was compressed to expel as much air from the lungs as possible and the upper ligature was firmly tied. With a third set of sterile instruments the abdomen was opened, the diaphragms were cut away from below and the ribs and sternum were removed in one piece to expose the thoracic viscera. The lobes of the lungs showing a maximum amount of disease were isolated by ligatures about the stem bronchi and removed to a sterile petri dish for bacteriological study. Portions of the tracheobronchial lymph nodes, the spleen and, where there was gross disease, the liver and hepatic lymph nodes were likewise removed. Zenker's fluid was then injected into the remainder of the lung through the trachea and the lower tracheal ligature was tied. This part of the lung and sections of the abdominal viscera were preserved for histological examination.

For bacteriological study, foci of infection were carefully dissected out under sterile precautions in the petri dish. The tissues were triturated in a sterile mortar with a small amount of physiological salt solution. When there was no reason to suspect contamination with secondary organisms, the triturate was used directly to seed Petroff gentian-violet-egg plates and for subinoculation. Tissues from animals which had died from intercurrent disease or were otherwise contaminated were subjected to the usual digestion treatment with normal sodium hydroxide followed by neutralization with normal hydrochloric acid. The neutralized digest was centrifugated, and the sediment taken up in a small amount of Proskauer and Beck's synthetic medium.

Petri-dish plates of both plain and sodium-taurocholate Petroff gentian-violet-egg medium were at first used for all cultures, but the latter was discarded after a time, as it was found that initial cultures grew poorly in the presence of the bile salt. With a capillary pipette, 6 or

8 drops of the untreated or digested lung extracts, respectively, were spread upon the surface of the culture media. With glass covers in place, the plates were incubated, medium surface up, for about 18 hours to permit evaporation of excess moisture, after which they were sealed with Petroff's rubber bands to prevent further desiccation and incubated at 37°C. in inverted position. To guarantee a sufficient oxygen supply the bands were readjusted every 3 or 4 days inside the incubator as Petroff recommends.

For animal inoculation the remaining portions of digested and directly triturated lung-tissue suspensions were pooled, and 2 cc. of the mixture were injected subcutaneously into the groin of another guinea pig. Portions of the spleen were treated in the same manner. In the first experiment 2 animals were used for subinoculation of each tissue, but in repeating the work one was used on account of the expense involved. Over 200 guinea pigs were employed for this purpose.

Detection of organisms by direct examination: In most instances smears stained by the Ziehl-Neelsen method were made of material to be cultured or subinoculated. From the entire first experiment no acid-fast bacilli were discovered. Histological sections were also stained in the same manner when the lesions showed sufficient activity to suggest the presence of organisms. In the first series, bacilli were found during the 9th and 10th months but not in the 7th month. No stains were examined at the other periods, as the lesions looked too unpromising. In the repeated experiment, however, bacilli were found in 6 of 10 animals killed before the 6th month and in 5 of the 11 animals showing subsequent spread of disease. The organisms were never numerous and were always hard to find even in active caseous foci. Much-Weiss stains in some instances seemed to reveal more beaded forms than the Ziehl-Neelsen preparations. Numerous gram-staining granules were often seen, but in the presence of dust particles and débris they could not be identified as Much granules.

In the control series of the original experiment, acid-fast organisms were found in only one animal, which was killed on the 12th month and showed an unusual circumscribed abscess, 7 or 8 mm. in diameter, in one of the caudal lobes. In the controls to the repeated experiment bacilli were found in 10 of the 15 animals in which stains were made. Only 5 of these occurred after the third month, and in 4 of the cases beaded rods were seen only in Much-Weiss preparations with none visible in the Ziehl-Neelsen preparations.

Subinoculations: Evidence of infection in the subinoculated animals, previously tested and found negative to 0.002 cc. O.T., was based upon the presence of either anatomical tuberculosis or upon one or more positive intracutaneous tuberculin reactions, at least four of which were usually made at monthly intervals. Traces of tuberculosis were often very slight, as the test-animals were not killed until 7 months or more after inoculation, to allow time for multiplication of small numbers of bacilli in the test material, as suggested by Petroff. As it happened, there was no alteration in the virulence of the R1 bacilli in any instance and the infection remained localized to the inguinal lymph nodes or, in rare instances, it spread to the spleen. After 7 months such infection in the lymph nodes often leaves little trace except fibrosis. Consequently the tuberculin reaction was occasionally positive in animals which showed only slight scars at the time of death. It frequently happened in the slight infections of the first series that a subinoculated animal would not react to tuberculin until two months after infection, when only a weak response would appear. The next test might be more vigorous but subsequent ones would be weaker and finally no reaction could be elicited. Such cases are included as positive results of subinoculation, although it is obvious that they must have been produced by the injection of small numbers of very attenuated organisms.

Subinoculation from practically all the dusted animals of the first experiment demonstrated that both their lungs and spleens harbored viable tubercle bacilli, although the organisms were not demonstrable by direct staining or culture. The lungs of the last 3 animals of the series killed during the 11th and 12th months showed no gross evidence of tuberculosis, and yet in two of them subinoculation still demonstrated organisms. In the remaining animal the portion of the lung chosen contained none, but the spleen produced a positive result. In the repeated experiment, in which the infection was heavier, subinoculation showed that viable bacilli were present in both lungs and spleens of all the animals killed from the first to the 15th month after infection.

In the undusted controls of the lightly infected first series, bacilli were demonstrated by subinoculation until 7 months after infection when they disappeared. In the more heavily infected second series they were demonstrable in all but one animal during the first 9 months. (No subinoculations were made from 4 cases with extensive nontuberculous pneumonias.) Unfortunately no subinoculations were made during the last 6 months.

Cultures: In a preliminary experiment two positive cultures had been obtained from 2 animals which were killed during the 15th month of the infection. These two guinea pigs had developed far-advanced silicotuberculosis with multiple cavities throughout the lungs. In the first experiment of this series in which the infection was so light, the lungs of all 25 animals were cultured and not a single growth of tubercle bacilli was obtained. In the repeated experiment with heavier dosage, 4 positive results were obtained from the lungs of 19 animals which were cultured. All 4 cultures were recovered from guinea pigs that had developed well-advanced silicotuberculosis. Two had survived 7 months, one 13 months, and the other 15 months after infection. In one of the 7-month animals the spleen also yielded a positive culture.

Of 25 attempted cultures on infection-controls from both series only 2 growths were obtained. In the first series a pulmonary tubercle, only 30 days old, yielded a growth, and in the second series a culture was obtained from a 90-day-old tubercle.

In a few instances cultures were obtained from subinoculated guinea pigs, but as these growths appeared identical with those from the original animals they need not be considered here. In addition 13 cultures were made on the lungs of another group of guinea pigs exposed to silica dust for one year and then infected by inhalation of a very small dose of R1 bacilli. Three of these were positive and one of 8 infection-controls to this experiment showed a growth of tubercle bacilli.

The colony structure, developing in these first generation cultures made directly from the animal body, was the same regardless of whether the material was obtained from a silicotic guinea pig or from a normal control. All of the 3 intermediate types of colony described in a previous communication (10) as characteristic of R1 tubercle bacilli were discovered, but the "burr" type was by far the most frequent. Typical R or S types were never observed. It was only after subculturing for five or more generations on artificial media that evidence of dissociation began to appear. There was nothing to indicate that variation in colony structure occurred more rapidly in cultures obtained from silicotic guinea pigs than in those from infection-control animals.

DISCUSSION

Those who have not had personal experience with the R1 tubercle bacillus will probably be surprised at the infrequency with which acid-fast bacilli have been discovered in smears of infected tissues and have

been recovered in cultures although their presence could be demonstrated by animal subinoculation. However, such findings are entirely in keeping with previous experience with this organism both in the Saranac Laboratory and elsewhere. Willis (12) has recently reported that he could obtain only 3 positive cultures from 34 animals infected subcutaneously with this organism although smears showed acid-fast rods in six of them. Sometimes cultures are positive when no organisms are detected in smears and *vice versa*. It seems probable that the Much-Weiss technique demonstrates more bacillary forms in the tissue than ordinary Ziehl-Neelsen staining. In tissues stained first by the Ziehl method, occasionally no organisms are demonstrable, but when the section is decolorized and restained by the other method many beaded-rod forms are not infrequently discovered.

As far as elucidating the relationship between silicosis and tuberculous infection is concerned, the evidence from this study has been largely negative. The original hypothesis, that the reaction of the tissues to silica might favor dissociation of the tubercle bacillus with the development of considerable numbers of virulent or S mutants, has not been substantiated. Nothing resembling a colony of S type, such as produced by repeated subculturing of a stock culture on Petroff gentian-violet plates (10), has been observed in the initial growths. Furthermore, dissociation has not taken place with any greater rapidity when such cultures were repeatedly transplanted on artificial media.

The virulence of the R1 organism is likewise apparently not permanently altered. While the bacillus continues to grow and produce slowly progressive tuberculosis in the silicotic animal, when it is transplanted into the environment of the normal tissues it again resumes its semisaprophytic characteristics and in most cases causes only involvement of the lymphatic system. Exceptional subinoculated guinea pigs have shown tubercle in the spleen but this occurred with no regularity and can probably be explained by the number of organisms injected.

It is noteworthy that the bacilli appear to be more abundant and are more readily cultured from the tissues of silicotic animals after at least 6 months of dust exposure. Willis found the same to be true of otherwise normal R1-infected guinea pigs, but this has not been so in the infection controls of these experiments. However, most of Willis's animals were allowed to live only 8 weeks, and he did not attempt to culture many which had survived for longer periods.

The fact, that subinoculation of portions of lung and spleen with no

anatomical evidence of tubercle frequently produces positive results, would indicate that stray bacilli may persist in the tissues after the nodular lesions have resolved and all traces of caseation have disappeared. This offers an adequate explanation for the recrudescence of the infectious element in the silicotuberculosis which sometimes manifests itself after most of the primary tubercles are apparently healed. In the majority of instances, however, the inhaled silica becomes incorporated in the developing tubercle, where it so alters the tissues that the bacilli do not die but continue to multiply and become the source of a slowly progressive, generalized infection.

When the infection immediately precedes the dust exposure there is a latent period of 5 to 6 months before appreciable extension occurs, but, when the dust exposure is continued for at least a year before infection, the bacilli appear to multiply rapidly as soon as they are implanted. This suggests that the factor which favors the growth of the bacilli is produced by interaction between silica and the tissues. Kettle (13) (14) observed that when mixtures of silica particles and tubercle bacilli were *injected* into the lungs or subcutaneous tissues, the number of organisms appeared to be rapidly increasing within one to three weeks. But injection of a sufficient quantity of fine silica particles will produce necrosis of tissue within 8 hours (4). By inhalation, several months are required to build up the same concentration of silica in the tissues. Therefore Kettle's observations are not at variance with those under discussion.

The general conclusion is drawn from these observations that inhaled silica dust alters the tissues so that they become more favorable to the growth of tubercle bacilli. The organisms themselves undergo no permanent change, so that when they are transplanted to a nonsilicotic environment they again resume their usual characteristics of growth.

SUMMARY

Two groups of guinea pigs were infected by inhalation with attenuated R1 tubercle bacilli, one with a small dose and the other with a large dose. Approximately one-half of the animals were then exposed for 8 hours daily to the inhalation of a high concentration of pure silica dust. The remaining animals were kept as infection controls. At 30-day intervals, during periods of 15 months, the animals from the dusted and control groups were killed. Portions of their lungs were removed under sterile precautions for both culture and subinoculation into other guinea pigs. The remainder of the tissues were fixed for histological study and the detection of tubercle bacilli.

In the undusted control animals the tuberculous infection developed in characteristic manner. Subpleural tubercles, which varied in number with the dosage, developed to the stage of caseation and then healed by resolution. After 7 to 13 months most of them had completely disappeared. The only other gross manifestation of tuberculosis occurred in the tracheobronchial lymph nodes. In the group exposed to silica dust the infection did not heal but tended to become progressive. With the lighter infection the resulting disease was not very severe, but with heavier dosage a massive silicotuberculosis developed in 12 to 15 months. Cavity-formation was a regular complication in the latter instance.

Tubercle bacilli were difficult to detect in sections or tissue smears. Positive cultures were only obtained in sporadic cases, but they were more frequent in the dusted series. Of 53 control animals cultured, 7.5 per cent were positive, while 16.1 per cent of 62 dusted animals gave positive results. The type of colony obtained in the first generation on artificial media was an intermediate "burr," more or less characteristic of the R1 organism and there was no indication that a coexistent silicosis favored dissociation and the formation of S or virulent mutants.

Subinoculation of portions of the lungs and spleen into other animals demonstrated that bacilli were present even though they could not be detected in smears and cultures. In many instances infection developed in the subinoculated animal where there was no demonstrable tubercle in the tissue injected. In the control series bacilli were detected 8 to 11 months after infection and then they disappeared. In the silicotic animal organisms were present in increasing numbers throughout the period of observation. Bacilli from progressive silicotuberculosis produced only characteristic, self-limited involvement of the lymphatic system in subinoculated guinea pigs.

This experiment has failed to substantiate the suggested hypothesis that attenuated tubercle bacilli produce progressive tuberculosis in the presence of silicosis because they are dissociated with the formation of an excess of virulent mutants. There has been nothing to suggest that the organism has been in any way altered. Apparently the silicotic tissue merely offers a more favorable medium for the continued growth of an acid-fast organism, which under ordinary circumstances is barely able to maintain semisaprophytic existence. It still remains to demonstrate whether tubercle bacilli implanted in silicotic soil suffer any degradation of virulence. This will have to be studied with organisms more virulent than the R1 strain which is already attenuated almost to the point of vanishing virulence.

BIBLIOGRAPHY

(1) GARDNER, L. U.: Amer. Rev. Tuberc., 1922–1923, vi, 163.
(2) KRAUSE, A. K.: Jour. Med. Res., 1916, xxxv, 25.
(3) GARDNER, L. U.: Amer. Rev. Tuberc., 1929, xx, 833.
(4) Unpublished data from Saranac Laboratory.
(5) GARDNER, L. U.: Amer. Rev. Tuberc., 1923, vii, 344.
(6) GARDNER, L. U., CUMMINGS, D. E., AND DOWD, G. R.: Jour. Ind. Hyg., 1933, xv, 465.
(7) GARDNER, L. U., AND DWORSKI, M.: Amer. Rev. Tuberc., 1922–23, vi, 782.
(8) GARDNER, L. U., AND CUMMINGS, D. E.: Jour. Ind. Hyg., 1931, xiii, 97.
(9) PETROFF, S. A., AND STEENKEN, W., JR.: Jour. Exp. Med., 1930, li, 831.
(10) DOWD, G. R.: Amer. Rev. Tuberc., 1935, xxxii, 50.
(11) GARDNER, L. U.: Jour. Ind. Hyg., 1932, xiv, 18.
(12) WILLIS, H. S.: Amer. Rev. Tuberc., 1933, xxviii, 884.
(13) KETTLE, E. H.: Proc. Roy. Soc. Med., 1930, xxiv (section on pathology, pp. 1 to 16)
(14) KETTLE, E. H.: Brit. Jour. Exp. Path., 1924, v, 158.

OBSERVATIONS ON MULTIPLE TUBERCULOUS CALCIFICATIONS[1,2]

HENRY C. SWEANY

Although pathological calcification is an old phenomenon, its mechanism and significance in human disease is by no means a solved problem. It is known to exist in widely different forms of pathological conditions resulting from degenerative changes within the body. These changes are death and necrosis of tissue, followed by encapsulation, and a gradual accumulation of fatty acids and acids of sulphur, carbon and phosphorus as a part of the process. It is not unlike the age-old phenomenon of the setting of cement or mortar. The soluble calcium unites with the various acids to form insoluble calcium soaps and inorganic salts. These, in turn, gradually take on "water of crystallization" until there is at first a drying, then a hardening of the central mass in the form of "limestone" ($CaCO_3$), "gypsum" ($CaSO_4$), and other such insoluble substances. The result may be a calcified tubercle, vascular plaque, phlebolith, calcified haematoma, etc., depending on the particular cause and localization. Of these various forms the tuberculous calcifications are unquestionably the most common and of the greatest importance.

Apart from the mechanism of formation, such calcifications may have another useful purpose, namely, to serve as "tombstones" in the ancient graveyards of tuberculosis, by a study of which we may gain more knowledge of the pathogenesis of the disease itself.

The first work of separation of calcified tubercles into special types began with the description of the primary infection by Parrot (1) in 1876, and repeated by Küss (2) in 1898. Then more recently the works of Ghon (3), Ranke (4), Blacklock (5), and others, have done much to explain the retrogressive primary tuberculous calcification and differentiate them from calcifications of reinfection.

The principal features given for differentiating the primary type of

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Presented before the Pathological Section at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 17, 1934.

tubercle from the reinfection type are, first, the heavy wall of broad fibrils of connective tissue in the capsule, called "specific capsule" by Ranke, with no perifocal inflammatory changes. In the perifocal region there is evidence of a complete resorption of exudate usually replaced by emphysema. The primary tubercle is also prone to develop bone-formation rather early in the region between the central calcified necrotic mass and the heavy capsule. This process is definitely an indirect metaplasia where the heavy fibrocytes lying next to the calcified caseum seem to be the precursors of the new bone-tissue. Sometimes the bone-formation involves most of the capsule. Complete knowledge of this transformation is still lacking. As the process ages, there is then an attempt to resorb the heavy capsule and the calcified caseous and osseous material.

It has been observed by Puhl (6), Pagel (7), Simon (8), and others, that such characteristics are not present in all calcified tubercles. They observed that calcified tubercles resulting from reinfection differed from the primary form. In reinfection tubercles, the capsule is usually thinner; the fibrils are also thinner and not so well hyalinized; there are usually remnants of perifocal infiltration, and very rarely has bone-formation been observed. Puhl (6) reported that 7 per cent of secondary or reinfection lesions showed bone, against 50 per cent for primary lesions. Usually also the secondary calcifications are multiple, more or less regional, and do not reveal the oblong or circular contours possessed by the primary lesions. In fact, most calcified acinous-nodose clusters are angular and have "jack-stone" appearance on X-ray examination, while primary tubercles only show irregularity late in their evolution.

In studying the pathological material of the Municipal Tuberculosis Sanitarium, representing multiple calcifications, it soon became evident that there can be no sharp division made between the primary and reinfection tubercles. Rather, it is a matter of two predominant types with all intermediate stages in between. A complete explanation of these facts can only be forthcoming when all the factors of infection and immunity are considered. Such factors seem to depend upon the primitiveness of the soil in which the tubercle is planted, the size of dosage, and the degree of allergy and immunity present at the time the seeding occurs. By correlating the finer differences of calcified tubercles with clinical, X-ray and other findings, however, it may be possible to throw some light on the unknown aspects of such tubercles as well as the pathogenesis of the disease itself.

Inasmuch as the ordinary primary tubercle consisting of one or two parenchymal foci is a rather constant pathologicoanatomical unit, and the greatest variability occurs in multiple calcifications, it seems that a study of this group should reveal the most information. Multiple calcifications may be classified roughly into five arbitrary groups. First, there is the true multiple primary form, caused by multiple seeding throughout the lung with tubercle bacilli. A second grouping is still vaguely understood but consists of a resolved pneumonic or multiple bronchopneumonic localization in different regions of the lung, perhaps not as a result of multiple seeding but as a diffusion of the focus over this widespread area after the first localization.

A third grouping includes those forms that resemble primary lesions in every respect but are unmistakably of a more recent formation than other primary lesions within the same body. In other words they seem to have been formed during an early haematogenous dissemination of the primary lesion before allergy has been completely developed. This ante-allergic period has been thoroughly described and worked out experimentally by Debré (9) and is also considered an important prognostic indication by Bernard (10), who states that the longer the time interval existing between the first localization and the development of allergy, the better the prognosis.

A fourth group includes a type of calcification that is obviously primary in some respects, but lacks many features of the primary type. This group represents transitions from lesions resembling a haematogenous seeding after a primary focus, through gradual and progressive steps to purely secondary lesions.

Finally, the fifth-group are those calcifications that result from seeding after allergy has developed. In general, they may be considered as calcifications of reinfection. This group is by no means simple and uniform. There may be calcifications as a result of late haematogenous dissemination; there may be calcifications from small acinous-nodose bronchogenic infiltrations; from a caseous endobronchitis; or there may be calcified infiltrations ranging from small nodular tubercles to very large masses. They are almost as variable in their number and location as are the lesions themselves.

In the first group we may consistently place all those true multiple primary foci. Ghon (3) records 23 of two or more foci in his series of 165. Only one of these, however, had more than four foci. It may be

seen from this that the true multiple primary foci are not common. In a large number of children with tuberculosis, one will occasionally find a patient with several hundred foci ranging in size from a millimetre to 1.5 cm. in diameter, and scattered throughout most of the commonly used portions of the lungs with numerous corresponding lymph-node calcifications along the bronchial trunks.

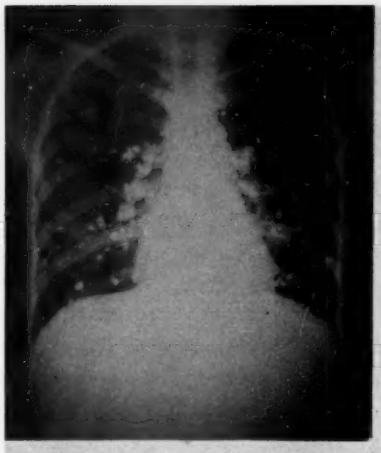
Such a case is one from our own Grand Crossing Dispensary, found routinely by Dr. Clara Jacobson, to whom I am indebted for the use of this reproduction. This child (*J. S.*, a 12-year-old female) left the city shortly after the X-ray picture was taken, and we are unable to report further upon it. (See figure 1, plate 1.)

Although it may be consistently argued that these calcifications are a result of haematogenous dissemination, the chief evidence is in favor of a multiple bronchogenic seeding. There are many reasons to suspect these of being true multiple primary lesions, but without a pathological examination, absolute proof is lacking and the evidence can only be considered presumptive.

In the second group are found some of the most interesting of all the forms of tuberculous calcifications. Here the deposits are almost innumerable; are confined to one region of the lung; resemble slightly the primary type; and are scattered throughout a parenchyma that shows evidence of having had atelectasis or a pneumonic consolidation at an earlier time. Although the lymph nodes toward and at the hilum are involved, they are usually insignificant and diminish in size toward the hilum. I have mentioned this phenomenon before with respect to certain adult primary lesions (11). Occasionally these lesions will soften in some central portion and go on into advanced disease. The following report illustrates the meaning:

E. S. (autopsy no. 396), a 15-year-old white male, was admitted to the Sanitarium in November, 1923, complaining of cough and expectoration for three months. The onset in August, 1923, was catarrhal, consisting of cough, moderate expectoration, loss of strength and weight, and night-sweats. Physical examination revealed dulness in the right upper quadrant and over the left dorsal region with bronchovesicular breathing over the right and "cog-wheel trend" over the left. The roentgenogram disclosed scattered calcified nodules but no recent parenchymal shadows. In February, 1926, however, there was a marked extension of the process into the parenchyma of the right with an annular shadow at the 3rd and 4th interspace. The process extended until death in March, 1930.

Fig. 1



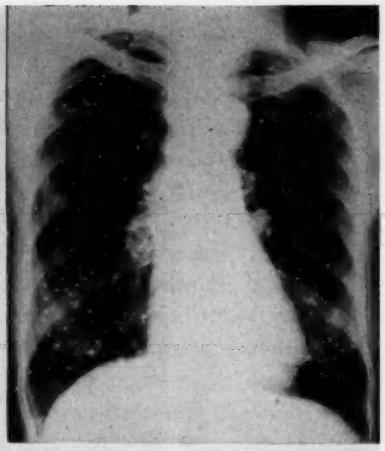


Fig. 2

Fig. 3

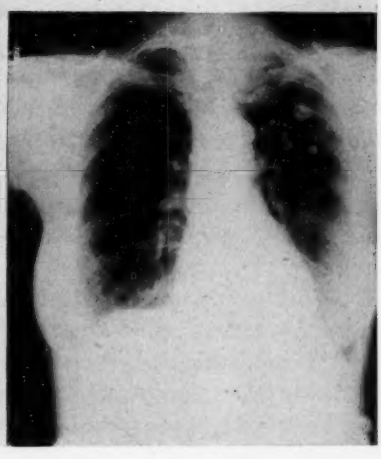


Fig. 4

PLATE 1

Fig. 1. Copy of roentgenogram of child, patient *J. S.*, Grand Crossing Dispensary, showing multiple basal calcifications, thought to be multiple primary foci.

Fig. 2. Patient, *B. R.*, Washington Boulevard Dispensary, showing a more uniform type of distribution of tubercles, thought to be a haematogenous dissemination, as the one illustrated in plate 3.

Fig. 3. Postmortem roentgenogram of patient *I. V.*, thought to be of mixed haematogenous and bronchogenic type.

Fig. 4. Roentgenogram of patient *Mrs. L.*, showing calcified round infiltrates of approximately thirty years duration.

The postmortem findings revealed that the right upper lobe was entirely destroyed by a moderate-sized cavity and extensive bronchiectasis. It occupied less than one-third its normal space. There were several clots of blood present in this cavity, and there was a communication to a smaller cavity in the upper part of the lower lobe. The middle lobe was very small and atelectatic, hanging on the middle border of the lung as a dense tongue-like appendage. There was a large cavity in the upper part of the lower lobe, measuring about 10 cm. across. This had heavy walls and the tissue beneath it was compressed. In the left lung there were two large thick-walled cavities in the upper part of the upper lobe. The lower cavity communicated with a cavity in the upper part of the lower lobe. The lingula was atelectatic and resembled the middle lobe on the other side. Throughout the upper part of the lower lobe there were scattering acinous-nodose and miliary tubercles. There was some hypostatic congestion in the posterior part. The hilum lymph nodes were moderately enlarged, but there were no hilum lymph-node calcifications. The two parts that were atelectatic,—the lingula on the left and the middle lobe on the right,—contained numerous calcifications. There were no other such lesions to be found anywhere.

Microscopic examination revealed an old atelectasis with bronchiectasis of both the lingula of the left upper lobe and the middle lobe on the right. There were many calcified tubercles having a rough resemblance to the primary type, although lacking the intense hyalinization of the capsules and also any hilum lymph-node complex. Some of these tubercles had apparently softened and ruptured.

Comment: It seemed quite suggestive that this patient had a benign type of infiltration in his middle lobe and the lingula on the left some years prior to his breakdown. This disease did not produce symptoms enough to cause the patient or his relatives to remember anything unusual. By August, 1923, however, some of the tubercles had apparently broken into a bronchus, or, in some other way, an infection had become localized in both lungs, so that "minimal" clinical disease was found on physical examination, and scattered calcifications throughout the midregions about the hilum were found on the roentgenogram. No excavations were observed until three years later. This was not typical of the accepted form of first infection, yet there was no other sign of a primary focus in the body. It may have been a reinfection following a very mild early infection.

It is no longer possible, however, to maintain that the Ranke theory (4) holds consistently in all forms of primary tuberculosis. There are many apparent exceptions especially as to adult primary foci in civilized countries.

Another patient ran a similar course, and we were able to correlate the history with the pathology in a similar manner, as follows:

J. L. (autopsy no. 639), a white female, 23 years of age, and of Irish parentage, was admitted to the Sanitarium in May, 1932. She was in contact with her sister who had tuberculous peritonitis three years previously, though the patient's trouble antedated her sister's illness. The patient's general health had been good. She went to high-school for three years, after which she worked as a comptometer operator for one year. She then married and kept house for four years. There is no history of dissipation or venereal disease. In the past she had measles, scarlet fever, whooping cough and mumps. The onset was catarrhal in April, 1928, followed later by an acute illness in May, diagnosed as pneumonia and pleurisy (right side). The symptoms were high fever, rapid loss of weight, 25 pounds in all, severe pain in the right side of the chest, chills and sweats, cough, expectoration, weakness, and loss of appetite. The acute symptoms lasted about two months but the pleurisy continued more or less constantly for one year. Later the sputum increased in amount and had a foul odor. Roentgenograms at this time prompted a diagnosis of lung abscess. There was a gradual improvement in strength and weight. After this there were two successive pregnancies, with a recurrence of symptoms each time, followed by improvement. The patient then continued well until two months before admission to the Municipal Tuberculosis Sanitarium, when, at the advice of a friend, she went to the Illinois Research Hospital where tubercle bacilli were found in the sputum.

On admission, physical examination disclosed nothing pertinent to the present report, but the roentgenograms revealed an irregular annular shadow in the right base, surrounded by numerous small calcified nodules, with early infiltration in both uppers. Before death two large cavities appeared in the upper lobes. The principal pathological findings (see plate 2, figures 1, 2, 3 and 4) were as follows:

In the right lower lobe were what appeared to be the oldest lesions in the lung. They consisted of numerous calcifications (approximately several hundred) measuring 0.5 to 5.0 mm. in practically every part of the lobe except in the middle, where there was present a large fibroid cavity, measuring 2.5 x 3.0 cm. This cavity was the thickest-walled of any excavation in the lung. The tubercles were well calcified and seemed to be of approximately the same age. There was a definite emphysema throughout the lobe with an occasional strand of fibroplastic tissue. Along the main bronchus toward the base was a definite dilatation. There were saccular cavities found at different points along the smaller bronchi in this lobe. There was a very small calcification in a bronchial lymph node near the hilum, about 1 mm. in diameter, and many others in the bronchial lymph nodes along the smaller bronchi. In both upper lobes there were moderately thick-walled cavities located along the subapical bronchi respectively, each cavity 2 cm. in diameter. Throughout the remaining portions of the two upper lobes and middle lobe were more recent tuberculous infiltrations, some of which were distinctly

bronchopneumonic in character. In the base of the left lower lobe were recent acinous-nodose infiltrations. In the main vessel toward the base in the left lower lobe was a recent thrombus that led to an infarction which was the immediate cause of death.

The microscopic examination revealed that the scattering calcifications resembled, but were not typical, of primary tubercles. The lymph-node calcifications along the smaller bronchi of the right lower lobe also resembled primary tubercles. The parenchyma showed more recently formed tubercles of various ages, some of which were resorbed except fibrous scars containing an occasional caseous focus with giant cells. The remaining portions of the parenchyma consisted of emphysematous tissue except where the large thick-walled cavity was situated.

In correlating the findings of this patient we suspect that the following conditions prevailed: that the first "cold" the patient had in April, 1928, was the first manifestation of tuberculosis; that the pneumonia of May, 1928, was the extension of this tuberculosis throughout the whole right lower lobe; that there probably were no older tuberculous foci of consequence, because there were no other lymph-node calcifications found anywhere in the body; that the excavation first called an abscess was the first tuberculous cavity appearing as the central focus of a benign acute tuberculous pneumonia that ultimately sloughed out into a cavity at one point but resolved at others; and that this lower lobe involvement was essentially the first group of daughter colonies of the infection that sloughed out as a cavity.

The other features of the history and pathology are uneventful. It is pertinent to consider how far amiss would be any consideration of a haematogenous seeding in these two cases, although from the roentgenogram alone such a conclusion may have been drawn.

In group three we wish to present an entirely different type of calcification. Here there is evidence of an old typical primary lesion; but there are also varying numbers of scattered calcifications that resemble primary lesions, but which are found by careful comparison to be of a more recent localization than the original. This is approximated by the degree of bone-formation and resorption of the capsule. Still more significant, these calcifications are rather uniform in size and are evenly distributed throughout the lungs, indicating that they were laid down at one time and may belong to the state of haematogenous dissemination after the primary focus and before complete allergy were established.

The first case is one furnished by Dr. H. D. Lees of Philadelphia, for the use of which I wish to express my appreciation.

The subject, a young male student examined routinely in survey work, disclosed nothing in the history to point to a severe primary tuberculous infection. The patient had "experienced rather severe and prolonged upper respiratory

Fig. 1

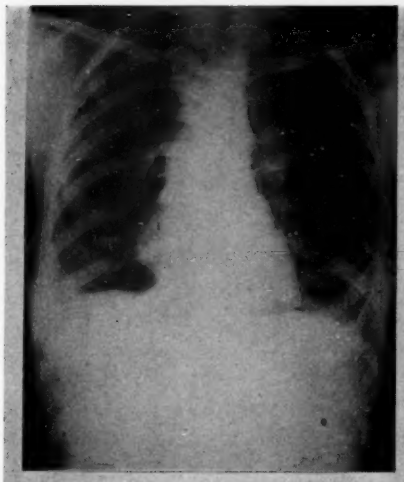


Fig. 2

Fig. 3

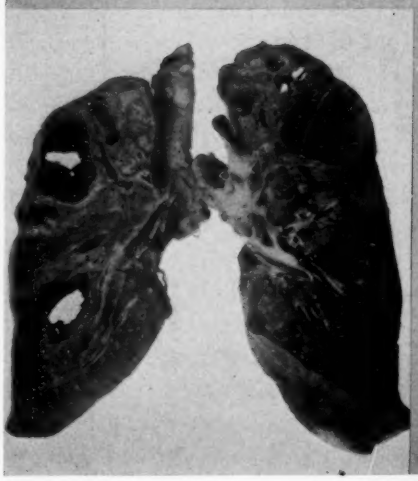


Fig. 4

PLATE 2

Fig. 1. Roentgenogram of patient *J. L.*, showing a linear shadow in right base with very fine multiple calcifications.

Fig. 2. Postmortem roentgenogram of the right base of the same case, showing many calcifications and the large central cavity.

Fig. 3. Gross photograph of a midsection of same case, showing the central cavity in the right base, and a few of the calcifications, with more recent spread to other parts of the lung.

Fig. 4. Microphotograph of a section of the right base, showing the type of calcification. Haematoxylin and eosin. $\times 3\frac{1}{2}$

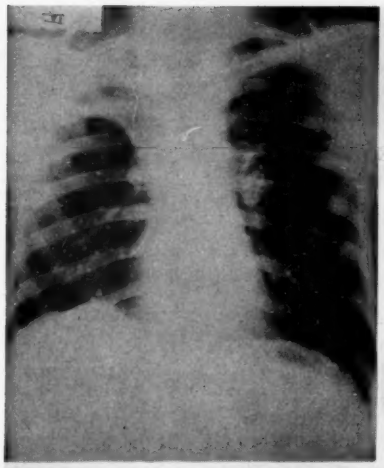
infections and was first observed [by Dr. Lees] as he was clearing up a basal bronchopneumonia."

The next case to be reported is loaned through the courtesy of Dr. Edward L. Quinn, of our Washington Boulevard Dispensary. It is an X-ray of a young woman, patient *B. R.*, found routinely in our Washington Boulevard Dispensary. Up to the present time she has not shown any symptoms of pulmonary tuberculosis. The X-ray reveals about 200 nodules throughout, with a few large calcifications along the main-stem bronchi. As the patient is still living, the evidence can be considered only presumptive, but it is almost identical to the next case, which we are able to give in detail. (See figure 2, plate 1.)

Case 2: W. B. (autopsy no. 642), a 35-year-old American of Norwegian ancestry, had a variety of occupations, mostly of a clerical nature. There had been no tuberculosis in his family and no history of contact. The onset was insidious in August, 1925, with fatigue, progressive shortness of breath, and semiproductive cough, which has persisted ever since with no increase in severity. From October, 1925, to February, 1926, he rested in bed, gained in weight, and felt generally improved. He then spent 14 months in the Woodman Sanatorium in Colorado, after which he was discharged as quiescent and returned to Chicago. While in the Woodman Sanatorium he had an X-ray picture taken that revealed many shot-like calcifications throughout, and a large cavity in the right upper lobe. Thanks are due Dr. C. E. Harris for permission to use this film. On August 29, 1928, the patient went on an automobile ride and was bumped against the top of the sedan. The next day he developed a severe haemorrhage (three sputum-cupfuls), and since then his fatigue and shortness of breath had returned. He entered our Sanitarium in November, 1928, and gradually became more dyspnoeic until death, five years later. (See figures 1, 2, 3, and 4, plate 3.) There was nothing pertinent in the extrapulmonary disease except a few very small ulcers in the ileum and appendix. *There were no tubercles of any sort in any of the parenchymatous organs.*

Postmortem findings in the lungs revealed numerous calcified and ossified primary tubercles in the inferior and superior right and left tracheobronchial, and in both right and left bronchial lymph nodes. Throughout the parenchyma of both lungs, scattered at regular intervals, were calcified nodular tubercles that were entirely encapsulated and had a yellowish appearance characteristic of primary lesions. There were approximately 150 of these tubercles in each lung. There did not seem to be any particular point of predilection for their location. The right upper lobe was markedly contracted and contained a healing cavity in the region of the subapical bronchus. There

Fig. 1



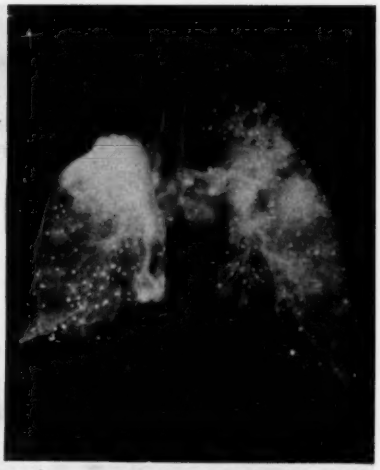
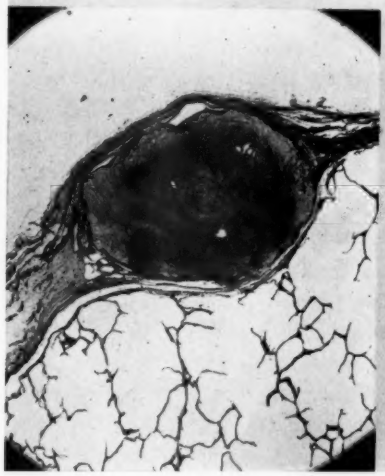


Fig. 2

Fig. 3



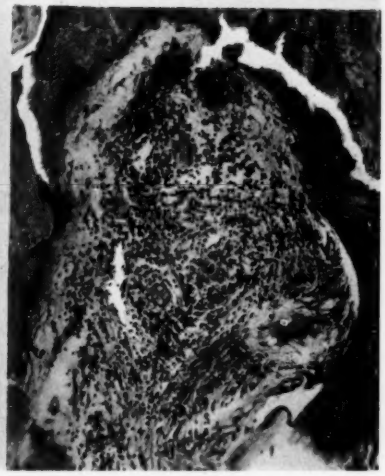


Fig. 4

PLATE 3

Fig. 1. Roentgenogram taken at Woodman Sanatorium, April 4, 1927, showing multiple calcified nodules scattered evenly throughout, with large cavity in right upper.

Fig. 2. Postmortem X-ray, taken seven years later, showing the fibroid mass surrounding the cavity in the right upper; the many shot-like nodules throughout both lungs; and the eroded calcifications at the hilum.

Fig. 3. Microphotograph of a peripheral, subpleural nodule, showing waves of calcification in the central caseum, and the thin ring of bone around the outside, with a greatly thinned-out fibrous capsule. Haematoxylin and eosin. ×10

Fig. 4. Microphotograph of one of the hilum calcifications, showing a total destruction of the capsule, with a replacement by bone and marrow tissue. Haematoxylin and eosin. ×95

was a small caseous centre measuring 3 to 4 cm. in the centre of this fibroid mass. At the apex of the right lower lobe was a more recent irregular cavity about 1.5 x 3 cm. Throughout the whole lower and middle lobes was a clearing acinous-nodose type of tuberculosis showing a marked scattering of fibrous tissue and almost a continuous spread of emphysema of healing, affecting one-half or two-thirds of the alveoli of this region. There was also an obliterative pleuritis surrounding this lung.

The left upper lobe contained some more recent nodular tubercles undergoing a clearing with resulting emphysema, some of which was bullous in nature. In the lingula and both bases the remaining normal tissue showed an extreme degree of acute emphysema. The lower part of the left lower lobe was similar to the right lower lobe. There were no fresh tubercles present. Death appeared to have been caused by a gradually developing dyspnoea resulting from the spreading infection.

After microscopic study of 13 different sections of different tubercles from this lung, it was concluded that the tubercles may be divided into two classes. The first is that represented by the large irregular mass at the hilum with a broken capsule and much ossification, and the other ones in the parenchyma represented by a well encapsulated type of tubercle with a rather even ring of bone around the calcified centre. There was only a very slight destruction of the capsule on the inner surface of these parenchymal tubercles. Perhaps the parenchymal primary focus, corresponding to those at the hilum, was sloughed out in the cavity in the right apex.

In summary, the case seems to represent a type of tuberculosis beginning in the right upper lobe and continuing as a flowing type of primary infection, leaving a typical calcified lymph-node complex in the hilum and a subsequent haematogenous seeding by the lesser circulation throughout both lungs (but nowhere else), that was far enough in the ante-allergic period to form tubercles resembling the primary type. Later there was an exacerbation in the right upper lobe that led to the formation of a large cavity. An acinous-nodose spread then occurred that involved most of the remaining tissue, thus accounting for the dyspnoea, emphysema and death.

Group four constitutes a type that represents a continuous and progressive seeding from a primary-like lesion through transition forms to secondary types. The evidence points as much to a bronchogenic seeding as to a haematogenous, although from a roentgenographic viewpoint it corresponds to the tuberculosa fibrosa densa of Bard (13).

I.V., a light brown colored girl, 20 years old (figure 3, plate 1), complaining of weakness, slight cough, and afternoon elevation of temperature, came to the Sanitarium, remaining six months, and seemed to have recovered. Two years

later, however, she developed a cough with an exacerbation of her symptoms of weakness, fever, night-sweats, haemorrhage, and a positive sputum. The roentgenograms revealed multiple calcifications in the upper parts of both upper lobes, more on the left, and somewhat irregularly distributed. These varied in size from 2 to 7 mm. in diameter and were irregular in outline. The patient went on to death, and at autopsy the calcifications were found similar to those already observed on the antemortem X-rays. The character of some of these lesions was essentially primary and most of them were about the same age. There was a moderately heavy capsule and definite ring of bone. With only slight resorption of the capsule. There were also transition forms of tubercles ranging from the primary-like focus and through to the recent terminal acinous-nodose clusters. There were a few terminal miliary tubercles in the spleen but the other organs were free from them.

Comment: To reconstruct the history of this patient and correlate it with the pathological features is difficult. Although it is not possible to say that the patient did not have a primary infection before, it seems probable that this infection was essentially a "flowing" type of primary focus and that the spread was gradual from the earliest lesions to the adjacent tissue by the bronchi. Whether the earliest localization was by the blood-stream or by bronchi cannot be determined. If by blood-stream it would presuppose a focus elsewhere in the body which was not found. It seems quite similar to the next case in which the process was more acute and in which we were able to follow the disease almost from its inception.

Case 2 is that of *E. V.*, a 21-year-old Filipino who came to the United States in 1927 to attend school (figures 1, 2, 3 and 4, plate 4). His aunt had tuberculosis but there was no other contact. Before he could enter school it was necessary for him to work, which he did in a very unsanitary laundry. On entering school in February, 1928, he began to spit blood. He finished his school-year and worked again during vacation. Soon he began to spit blood again but paid no attention to it until he developed a severe pain in the abdomen, at which time he went to Cook County Hospital, where a diagnosis of tuberculosis was made. He was then sent to our Sanitarium and became progressively worse, dying in March, 1931, four and one-half years after the first symptoms.

The predominant clinical findings on admission to the Municipal Tuberculosis Sanitarium were an impairment of resonance over the upper parts of both lungs. There was a *suppression of breath-sounds* with prolonged expiration, especially over the right. There were râles over these regions also.

The first roentgenogram revealed chiefly mottled areas that extended up to the apex from the hilum on the right. There was a gradual increase of similar

densities on the left, although the left side was never as markedly infected as the right and it appeared much later. The sputum was never positive by direct or concentration examination. Only on culture and animal inoculation were tubercle bacilli found during life.

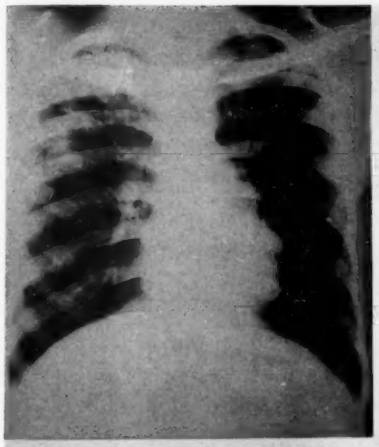
The postmortem findings in the lungs were that the entire right upper lobe had a grayish appearance with small specks of coal pigment throughout and caseous tubercles situated near the ends of the main bronchi. There were fibrocaseous plugs extending down the lumina of these main bronchi. There were a few tubercles in the left upper lobe and a few smaller ones throughout the base of the right upper lobe. The hilum lymph nodes were anthracotic but not tuberculous.

There were also a few scattered nodular tubercles in the spleen, liver and kidney. There was an advanced ulcerative enteritis and a moderate *tabes mesenterica*. The microscopic examination of the lung sections revealed lesions ranging in age from early calcification to recent caseous infiltrates. The most markedly calcified lesion was found in the right apex. It measured about 2 mm. in diameter. Around this are found several larger ones, nodular in form and with a moderately dense capsule, but there seemed to be a tendency for the process to spread through the capsule into adjacent tissue and bronchi. Some of the larger bronchi contained casts of fibrocaseous material for several centimetres as a descending endobronchitis. It was definitely descending in this case because the lower end was softer, less fibrotic, and the layers of fibrous tissue appeared as a gradually accumulating network that bent downward and became of a more recent formation toward the larger bronchi. Out in the parenchyma of the middle lobe and base of the right upper were fibrocaseous tubercles of more recent formation. In the left apex there were a few tubercles that were beginning to calcify but of much more recent date than those in the right apex. The extent of the involvement in the left was also much less.

Comment: This patient either contracted the disease from his aunt or from an unknown source just after coming here, because the ages of the lesions indicated that the process was relatively recent. In spite of the fact that he did not have a tuberculin test, it was scarcely probable for him to have acquired an earlier infection, because none was found in any of the common localizations, and the character indicated that this was probably a part of the primary process or the late stages of it. If the first localization in the right was by the blood-stream from another recently formed primary process, certainly some of the other foci seem to be by direct extension or bronchogenic spread. There was, therefore, a haematogenous dissemination, as proved by the tubercles in the spleen, liver and kidney, of which some of the lung tubercles were a part, and later a mixed process where there was definite evidence of bronchogenic spread.

The lesion in the right apex appeared to spread gradually beyond the capsule

Fig. 1



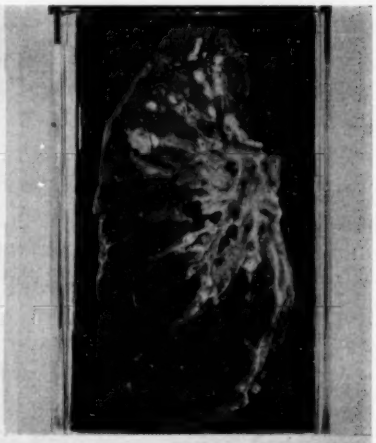


Fig. 2

Fig. 3

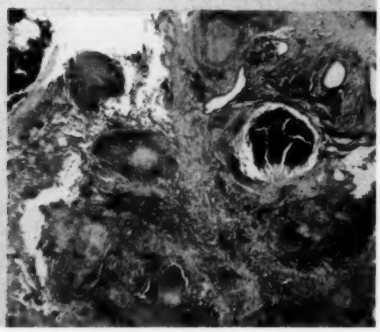


Fig. 4

PLATE 4

Fig. 1. Roentgenogram of *E. V.*, case 2, group 4, taken August 23, 1930, showing diffuse infiltrates in right upper.

Fig. 2. A sagittal section taken of lung after death, showing small calcified foci in apex, with a descending caseous endobronchitis and more recent nodular tubercles toward the base of the lobe.

Fig. 3. Microphotograph of a bronchus containing plugs of fibrocaseous material. Haematoxylin and eosin. $\times 3\frac{3}{4}$

Fig. 4. Microphotograph of the type of calcified tubercles in the right apex. Note the perifocal spread around the calcification. Haematoxylin and eosin. $\times 9$

of the tubercle and then involve the surrounding tissue and enter the smaller bronchi. Calcification likewise extended from the oldest tubercle in the apex and appeared, in a slight degree, in one of the smaller bronchioles. There was a gradual spread downward into the larger bronchi and into uninvolved lung tissue. This mode of spread resembled slightly the mode described by Loeschcke (12). It differs, however, in the steady progression without the fine and coarse dissemination, described by that author.

Such a reconstructed history of a recent and active case will perhaps throw some light on the pathogenesis of nodular apical calcifications. Should the course of this patient have been more favorable and the many nodular tubercles healed, it would have fitted into the group called successively by Bard (13), Borrell (14) and Neumann (15) "*tuberculosa fibrosa densa.*" Most of such tubercles, however, break into small oblong cavities before calcification is complete.

In the fifth and last group are the calcifications of tubercles that have been formed after establishment of allergy either by bronchogenic seeding or by the way of the blood-stream. It must be pointed out, however, that there may be transition forms that may be placed equally well in either group. There is no sharp line of demarcation but a gradual transition as the patient's basic reactability changes resulting from the infection.

Case 1 of this group represents the calcification of a long-standing healing pulmonary tuberculosis. The patient, *E. J.* (autopsy no. 423) was an American, 28 years old, of Scandinavian extraction. There was no known contact with tuberculosis. The first suggestion of anything wrong was a swelling of the lymph nodes of the neck four years before admission. These disappeared on "treatment with iodine." He then noticed a tiredness and weakness with a cough and some expectoration. The weakness continued until he sought medical advice, at which time he was referred to the Municipal Tuberculosis Sanitarium with a diagnosis of pulmonary tuberculosis because of a sputum positive for tubercle bacilli. Subsequently he was found also to have an Addisonian complex, from which he never recovered.

The autopsy revealed, in addition to a partly calcified destructive tuberculous disease of the adrenals, scattered calcified tubercles throughout the upper parts of both lungs. There was one definite old primary complex with a large number of more recently calcified tubercles of a definite secondary character, and clearing acinous-nodose clusters throughout the upper halves of both lungs, leaving a marked emphysema of healing. At various intervals could

be found the secondary calcifications, many of which were discrete and round, suggesting a localization by the blood-stream. There were also many small angular ones that may have resulted from a bronchial seeding.

Comment: It seems justifiable to assume that this patient had an old primary process of many years' standing, perhaps dating from childhood; that about four years before admission there occurred a haematogenous scattering of tubercle bacilli from this old focus, chiefly by the lesser circulation, resulting in a few foci in the lymph nodes of the neck and the adrenals, and a large number in the upper parts of the lungs.

The pulmonary localizations ultimately spread out into the bronchi from which acinous-nodose formations occurred and which was the cause of his clinical pulmonary tuberculosis. These foci healed or were healing, leaving some calcifications and emphysema causing his dyspnoea. This became aggravated by lowering blood-pressure as a result of the destruction of the adrenals. The calcifications were a mixture of a few primary lesions with a large number of the reinfection type.

Case 2 is another quite similar to case 1. *E. J.* (autopsy no. 593), a female born in Sweden in 1891, came to America at the age of 16. (See figures 1 and 2, plate 5.) The pertinent part of the history is that the patient had had influenza in 1919, after which she never felt well. Just prior to this time she had a brother die at the Municipal Tuberculosis Sanitarium of pulmonary tuberculosis.

Nine years previous to admission, in October, 1933, the patient had a breakdown with a mild attack of influenza, after which she tired easily. She stopped work for two months and went to Ohio to visit her brother. On the train she caught a cold, and following this she seemed to be very susceptible to colds. After this visit she returned to housework, at which she continued for two years when she again noticed that she was very easily tired. For the next two years, however, she felt fairly well, but five years before admission she caught another cold, and two weeks later had a bad cough. She coughed up about a half-cup of blood on two occasions. Later she developed a severe bronchitis and coughed a great deal. For the past 14 months she has been confined to bed except to get up for meals. However, she has not lost weight at any time during the nine years since her first breakdown; rather, she has gained in weight. She has been more or less under observation for nine years at the Wabash Avenue and Stock Yards Dispensaries.

The pertinent findings in the postmortem examination revealed a large mass of calcified lymph nodes in the mesentery and in the peripancreatic region. There were numerous disseminated calcifications in both upper lobes. The whole left lung was a mass one-half normal size, consisting of multilocular

cavities throughout with very slight caseation. The right lung had a few recent implantations of bronchogenic origin. Although numerous calcifications are seen in both uppers, none is found at the hilum. This is compatible with a reinfection type of involvement.

The microscopic examination showed an old large cluster of markedly eroded primary lesions in the abdominal lymph nodes with definite "secondary type" of calcifications in the lungs. These were of various ages, ranging from dense calcified tubercles to soft caseous and ulcerative lesions. They were apparently evenly distributed on both sides although a huge cavity on the left had occurred.

Comment: The history of this patient seems to suggest that she received her primary infection from her brother by the gastrointestinal route. Following this she developed "influenza" which may have been the symptom of the primary lesion in her abdominal lymph nodes. After this there was the continuous haematogenous seeding to the lungs by the lesser circulation and the vague symptoms of occult tuberculosis, manifested by repeated colds and a sense of ill-being, until the pulmonary lesions broke out into open disease. Most of the calcified lesions in the upper parts of both lungs we feel justified in considering as haematogenous dissemination from the older abdominal primary.

Occasionally fibrocaseous endobronchial plugs will become calcified as casts of the bronchi in which they have formed. The next report represents such calcification.

Case 3: R. R. (autopsy no. 436) represents an unusual type of multiple calcification in which fibrocaseous bronchial casts have become calcified. These casts may have been formed similarly to those reported in case 2, group 4.

There is no need to give the history of this patient except to state that he was a man 64 years old. He had a healed fibroid tuberculosis, as will be evident from the postmortem findings. Only the pertinent findings in the lungs will be described as the others have no bearing on the subject under discussion.

In the right lung at the base posteriorly and just beneath the pleura was found a calcified, ossified tubercle 5 x 7 mm. in diameter. There were a few smaller calcified and ossified nodes up toward the hilum. On the right side of the hilum there was a large calcified lymph node. There was also a large lymph node up along the trachea. Both of these measured about 1.5 x 2.5 cm. There were various small calcified clusters in the upper parts of both lungs. The whole lung was emphysematous and was characteristic of healing tuberculosis. There were numerous encapsulated, caseous and calcified tubercles throughout, particularly in the terminal bronchi. Some of these tubercles conformed to several branches of bronchi and were really calcified casts of

Fig. 1

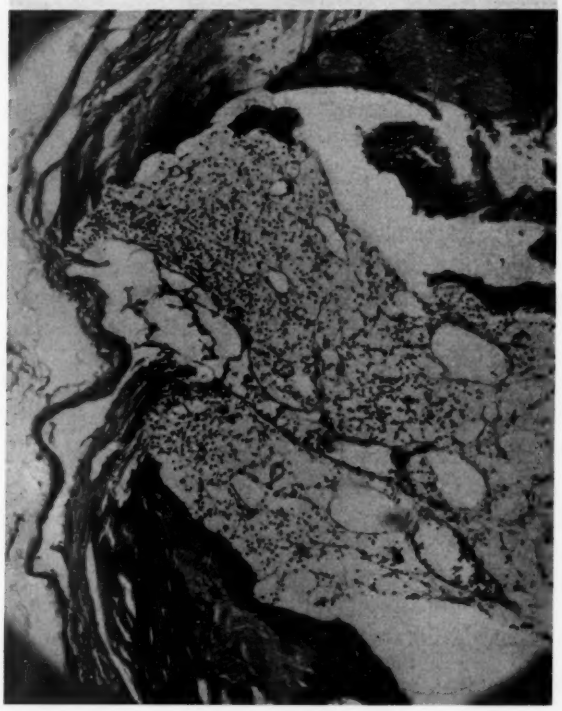


Fig. 2

PLATE 5

Fig. 1. Microphotograph of lung tubercles of patient *E. J.*, case 2, group 5, showing the secondary type, encapsulated with thin strands of connective tissue, and one showing a rupture. Haematoxylin and eosin. ×4½

Fig. 2. Microphotograph of an old primary in the abdominal lymph nodes, showing the destruction of the heavy-walled capsule at one point, with bone- and marrow-formation. Haematoxylin and eosin. ×106

them. They varied from 1 to 5 mm. in diameter and 5 to 30 mm. long. Some of the bronchi appeared to terminate in small stellate scars. Usually from the tubercle or scar toward the hilum the principal bronchial rami were moderately dilated. There was one scar on one of the branches of the posterior apical and one on the horizontal ramus, respectively. In the middle lobe these bronchial casts were more prominent. There were two or three near the surface that occupied several branches of the terminal bronchi. In the lower lobe there was only one little cluster of tubercles in the upper part along the spinal border and a calcified tubercle at the base. In the left lung the first and most important thing was a fibrotic mass occupying practically the whole region of the subapical bronchus of the upper lobe. In this mass were numerous tubercles, practically all encapsulated. Some had small early deposits of calcium. There was one large one that was soft and cheesy in consistency. The bronchi draining this area were all markedly dilated and only extended to 2.5 cm. from the pleura where they terminated abruptly in this scar. The other bronchi were all similar to those found in the middle lobe. Many of them terminated in fibrocaseous casts. This same thing applied to the left lower lobe. The tubercles were greater in number and size, however, on the terminals of the first posterior branch.

Comment: The type of calcification represented in this specimen is perhaps an advanced stage of the bronchial casts shown in case 2, group 4. Such casts usually terminate in a larger peripheral tubercle. When this does not happen, however, it cannot be differentiated from an ascending caseous bronchitis that is due to aspirated mucus and tuberculous pus.

Case 4 is a healing acinous-nodose tuberculosis in patient, *G. I.* (autopsy no. 516) undergoing four years' treatment for far-advanced pulmonary tuberculosis with calcification of many acinous-nodose clusters of tubercles. The patient finally died of bronchogenic carcinoma. In practically all healed advanced disease this form is found.

The last type of multiple calcifications to be reported are what may be termed calcified infiltrates. Infiltrates of large dimensions most often become excavated into cavities, but occasionally they remain intact. In a previous work, I (16) reported such a primary calcified infiltrate before rupture in a child dying of haemorrhage after tonsillectomy.

Case 5 represents a cluster of calcified infiltrates (figure 4, plate 1), found in a woman 52 years of age, and treated for active tuberculosis thirty years before. As the stereoroentgenogram shows, this type is clearly a calcified cluster of infiltrates resulting from a bronchogenic reinfection along the main stems of the left subapical bronchus.

Finally, I wish to mention the fact that there are other forms of multiple calcifications within the chest that may be mistaken for calcified pulmonary tubercles. These include calcified plaques in tuberculous pleuritis and calcified encapsulated haemorrhage within the lung or pleural cavity. Such lesions, however, are outside the scope of this work.

DISCUSSION

After studying multiple pulmonary calcifications of various types, it may be concluded that any parenchymal tuberculous lesion that does not excavate into a cavity may become calcified, if the time is sufficiently long. We may visualize the calcifications, therefore, as "fossil" lesions that thrived once as active infiltrations, followed by caseation and encapsulation. The determination of origin, age, and character of such lesions, however, cannot be done by a study of roentgenograms or history alone, but only by a careful clinical and X-ray examination, correlated with a postmortem X-ray and pathological study.

Rather arbitrarily, I have arranged the material into five groups, although this is more for convenience than an attempt to form a distinct classification. On the whole the work stands out as a group of indestructable milestones in certain phases of the pathogenesis of tuberculosis.

Perhaps the most common form of multiple calcification is the calcified acinous-nodose clusters of tubercles representing the most common form of tuberculous reinfection. Such tubercles are frequently found in healed minimal and moderately advanced lesions of long standing. Occasionally they appear in healed advanced disease. They are usually asymmetrical, angular, poorly encapsulated, and poorly infiltrated with calcium. Next in importance is the haematogenous seeding which is quite variable as the various reports indicate.

Passing over all the acute haematogenous forms, such as the generalized miliary and *typho-bacillose* of Landouzy (17), we find that there are chronic and benign forms of blood-borne infection.

The older work of Bard (13), Piéry (18), amplified by Borrell (14), and recently revived by Neumann (15), considers that the haematogenous origin of pulmonary localizations is common and that the latter are to be found in calcified residues as *tuberculosa miliaris discreta, tuberculosa fibrosa densa,* and *tuberculosa fibrosa diffusa,*—a series of complex terms for increasing calcification and fibrotic densities in the upper parts of the lungs resulting from haematogenous spread. A benign haematogenous

miliary form was termed *granulie* by Delarue (19) and *phthisie froide* by Bazin (20) and other French clinicians.

Huebschmann (21) has also shown how the haematogenous seeding may proceed in showers from the apex downward; that they decrease in size toward the base; that the fewer the number in the apex the larger they are; and that on excavating they tend to form thin-walled and punched-out cavities. Lydtin (22), among others, has recently pointed out anew the benign character of these forms. In this same category may be placed the chronic haematogenous dissemination of Schürmann (23), who applied the term from earlier work of Borrell (14). Much of this work indicates that a great deal of reinfection is probably due to the haematogenous route, but the proof is always difficult to establish and is almost entirely dependent on indirect methods, as emphasized by Huebschmann (21).

Since it has been established by complete reports in this presentation that certain forms of bilateral calcifications can only be haematogenous, it follows that the early bilateral seeding coming at one time or in showers, as suggested by Huebschmann and others, has been confirmed.

While it must be granted also that isolated unilateral localizations may occur by the blood-stream, particularly in the apex, and in certain regions of the lung, as suggested by Huebschmann, the majority of asymmetrical seedings must be looked upon as bronchogenic until more evidence is produced than we have at present.

Some forms of asymmetrical seeding appear to be a type of calcification resulting from a complete or partial resolution of an infiltrating benign type of lobar tuberculous pneumonia. This type seems to occur as a part of primary infection or an infection on a host having had only a very small and insignificant primary. Such benign forms are perhaps represented by Eliasberg and Neuland's (24) *epituberculosis* in children, and by Ornstein's (25) "acute benign" types in adults. There is no doubt that the forms reported differ from the usual tuberculous pneumonia, in that there is not the diffuse caseation and ulceration. Rather, there seems to be a diffuse lobar consolidation with a tendency of the bacilli to localize in scattered foci. The intervening tissue resolves, leaving an emphysema of healing with the scattered foci of primary-like caseous and calcified lesions throughout. Occasionally, some of the larger foci promptly break down into cavities while others soften and break down at intervals later or remain as multiple healed calcified nodules. To my knowledge the pathology of this form has not been

described before. There may be a tendency to consider this form of benign process as a perifocal allergic response. Such a position, however, is untenable because of the even distribution of foci throughout the involved area which means the actual presence of tubercle bacilli, either in reduced numbers or of attenuated virulence. There is apparently no way of explaining the phenomenon by a change in the host, therefore we must consider the other partner in the duel—the parasite.

It is possible, therefore, that the acute pneumonic consolidation may be due to atypical forms but are not sufficiently protected to survive and cause typical caseation, as in a true caseous pneumonia. The only other explanation is to assume an inspiration of a few bacilli into each of several hundred foci and around each of which there forms a perifocal reaction. A better knowledge of the tubercle bacillus may help to explain these interesting phenomena. It is my observation also that there is not a fixed form of benign lobar pneumonia, but a series of transition forms from the so-called benign types through to the most caseous types.

Regarding the pathogenesis of many of the forms formerly described as *tuberculosa fibrosa densa* and *diffusa*, I believe that the strictly haematogenous origin of all of these forms is open to question. True, most of them have a haematogenous aspect, but the encroachment on bronchi by the formation of such large masses can scarcely by avoided. The possibilities of this are plain from case 2, group 4. In some cases the haematogenous origin seems to be the only possible source, yet the calcifications do not vary greatly from those cases in which the route seems to be suggestive of a bronchogenic origin. We must bear in mind that bronchogenic seeding may simulate the haematogenous and *vice versa*, and that seeding may come by both routes simultaneously.

There are other types of multiple calcification from obvious haematogenous seeding, in which the pathogenesis, although obscure, may be partially understood. The uniform seeding by round shot-like nodular tubercles, that are occasionally seen, is obviously not on the same basis as any of the groups listed above. In this type there is a strong resemblance to primary tubercles microscopically. That they are haematogenous, there is little doubt. They are evenly distributed throughout and they may have been laid down during the ante-allergic period of the disease when the allergy-immunity complex has not been well developed. This is manifest, first, because the tubercles resemble the primary type in every way. There are usually two ages of "primary" tubercles pres-

ent, a true early single primary and then the many small primary-like lesions. Again the localizations extend evenly all the way to the base. In haematogenous seedings in late reinfection, there is a tendency for the seeding to be more exaggerated in the upper parts of the lungs.

CONCLUSIONS

1. A study of multiple calcifications, selected from over 600 autopsies and various dispensary and hospital patients, has been reported.

2. Calcifications may result from any type of encapsulated tuberculous focus; namely, multiple primary seedings; scattered foci occurring in a resolving benign type of tuberculous pneumonia; in a haematogenous seeding occurring in the ante-allergic period of the secondary stage of the primary; in various transition types from the primary into reinfection; in haematogenous reinfection; and in the healing of any form of tuberculous nodule or infiltrate arising from bronchogenic spread.

3. Calcification may never occur at all in progressive tuberculous reinfection, and may occur only slightly or not at all in many massive primary infections. In both types, calcification seems to occur only in older lesions that have been well encapsulated. Inasmuch as the primary lesions are better encapsulated, they have a greater tendency to calcify. Nevertheless any secondary type of caseous lesion that ultimately heals will also calcify. It follows that patients who have recovered from tuberculosis will show calcifications from not only the primary infections, but also the reinfection in which large-sized caseous lesions existed.

4. The differences between the primary and the reinfection tubercles are reflected roughly in their calcified and ossified forms, apparently changing from a primary type to a secondary type, and gradually, with the development of allergy.

5. By correlating the history, antemortem and postmortem roentgenographic findings, and the pathological changes in multiple calcified lesions, it is possible in many cases to determine not only the character of the various lesions themselves, but also obtain an idea of the mechanism of the process leading up to their formation.

REFERENCES

(1) PARROT, J. M.: Compt. Rend. Soc. Biol., 1876, p. 308.
(2) KÜSS, G.: De l'hérédité parasitaire de la tuberculose humaine, Paris, 1898.
(3) GHON, A.: The primary lung focus of tuberculosis in children, London, 1916.
(4) RANKE, K. E.: Ausgewählte Schriften zur Tuberkulose-Pathologie, Berlin, 1928.

(5) Blacklock, J. W. S.: Tuberculous disease in children, London, 1932.
(6) Puhl, H.: Beitr. Klin. Tuberk., 1922, lii, 116.
(7) Pagel, W., and Henke, F.: Lungentuberkulose. In Henke and Lubarsch, Handb. d. spec. path. Anat. u. Hist., iii, pt. 2, Berlin, 1930.
(8) Simon, G.: Beitr. Klin. Tuberk., 1927, lxvii, 467.
(9) Debré, R., and Bonnet, H.: Compt. Rend. Soc. Biol., 1922, lxxxvii, 449.
(10) Bernard, L.: Les débuts et les arrêts de la tuberculose pulmonaire, Paris, 1931.
(11) Sweany, H. C.: Amer. Rev. Tuberc., 1933, xxvii, 575.
(12) Loeschcke, H.: Beitr. Klin. Tuberk., 1928, lxviii, 251.
(13) Bard, L.: Les formes cliniques de la tuberculose pulmonaire, Paris, 1927.
(14) Borrell: Tuberculose pulmonaire experimental, Ann. l'inst. Pasteur., 1893, vii.
(15) Neumann, W.: Die Klinik der tuberkulose Erwachsener, ed. 2, Vienna, 1930.
(16) Sweany, H. C.: Journal-Lancet, 1933, liii, 393.
(17) Landouzy, L.: Presse Méd., Paris, 1908, xvi, 681.
(18) Piéry: La tuberculose pulmonaire, Paris, 1910.
(19) Delarue, J.: Les formes anatomo cliniques des granulies pulmonaires, Paris, 1930.
(20) Bazin: Quoted by E. Sergent, Les réreils d. l. tuberculose pulmonaire chez l'adulte, 1933, p. 28.
(21) Huebschmann, P.: Pathologische Anatomie d. Tuberculose, Berlin, 1928.
(22) Lydtin, K.: Klinische Untersuchungen über hämatogene und bronchogene Formen der Lungentuberkulose, Leipzig, 1932.
(23) Schürmann, P.: Virchow's Archiv., 1926, cclx, 66.
(24) Eliasberg, H., and Neuland, W.: Jahrb. f. Kinderhk., 1920, xciii, 88.
(25) Ornstein, G. G., Ulmar, D., and Dittler, E. L.: Amer. Rev. Tuberc., 1931, xxiii, 223.

THE PHARMACOLOGICAL ACTION OF TUBERCULOPROTEIN IN NORMAL AND TUBERCULOUS ANIMALS[1]

M. I. SMITH[2]

Perhaps the most interesting phenomenon in the reactions of the tuberculous organism is the latter's response to the injection of certain products derived from the tubercle bacillus commonly referred to as tuberculin. The tuberculin reaction, which was first described by Koch in 1891, is manifested in three ways; namely, by a local reaction of various degrees of inflammation at the site of injection, by a focal reaction characterized by hyperaemia and increased vascularity around the tubercle, and lastly by constitutional reactions of varying degrees of severity. These reactions, as is well-known, do not by any means run parallel and our knowledge as to whether or not they are manifestations of one and the same process is far from complete.

The question as to the nature and mechanism of the tuberculin reaction has received much attention at the hands of the immunologist, attention having been focused primarily upon the manner in which the hypothetical poison or toxin is liberated in the cellular interaction with tuberculin. The questions as to how this toxin produces its effects, what tissues or organs it affects, and the manner in which it does this, have received but secondary consideration. It is true that an attempt has been made to answer some of these questions in connection with the local cutaneous reaction and to some extent also in connection with the focal reactions, the explanations being based again largely upon the antigen-antibody conception. Indeed, some observers have been inclined to place the tuberculin reaction in the same category as the anaphylactic reaction, a supposition upon which much doubt has been cast but despite which it still persists in some quarters.

The constitutional or general reaction to tuberculin seems with few exceptions not to have been considered in the light of a pharmacodynamic problem seeking to elucidate the action of tubercle toxin in the

[1] A preliminary report of this paper, the publication of which has been delayed, was presented at the 25th annual meeting of the National Tuberculosis Association in 1929.

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tubercle-infected organism. The mistaken notion that products derived from the tubercle bacillus can exert demonstrable effects in the tuberculous organism only has probably served more than anything else to deter from giving the matter the pharmacological consideration it deserves. This, however, is not true, for, as pointed out by Kirchheim and Tuczek (1), and more recently also by Seibert (2), and the writer (3), tuberculoprotein possessing all the characteristics of tuberculin has a definite and considerable primary toxicity in animals free from tubercle, and, it should be added, in animals which are normally susceptible to the tubercle bacillus such as the guinea pig and rabbit, as well as in such animals as the rat which is relatively insusceptible to the effects of the tubercle bacillus. Furthermore, until recently, there has been no tuberculin available for pharmacological study free from the complicating constituents and degradation products commonly employed in the media upon which the tubercle bacillus is permitted to grow and from which tuberculin is usually made.

The recent successful preparation of a highly active and relatively pure tuberculoprotein possessing all the characteristics of tuberculin, and the finding that it has a definite primary toxicity in the nontuberculous animal, has made it both possible and desirable to investigate its pharmacological action in the normal and the tubercle-infected animal. Accordingly this paper concerns itself with some of the pharmacological effects of tubercloprotein "304-F" in the normal and tuberculous rabbit and guinea pig.[3] Since the most pronounced effect of the tuberculoprotein in the tuberculous animal appears to be circulatory failure it appeared desirable to make a special study of the action of this substance on the circulation in order to ascertain the cause of the circulatory collapse.

Kirchheim and Tuczek (1) found that Old Tuberculin injected intravenously into guinea pigs is from 10 to 20 times as toxic in tuberculous as compared with nontuberculous animals.

Califano (4), in 1925, studying the action of Old Tuberculin on the arterial pressure of tuberculous rabbits found that an intravenous injection of 5 cc. Old Tuberculin produced a slight and transient rise in blood-pressure. The same effect was also obtained in nontuberculous rabbits. A sterile concentrated glycerine-bouillon, similarly injected,

[3] For further details concerning the preparation of "304-F" the reader is referred to papers by Long and Seibert (10). The material used in this work was furnished by the Committee on Medical Research of the National Tuberculosis Association.

produced a fall in blood-pressure in both tuberculous and nontuberculous rabbits. He considered the lowered blood-pressure to be due to the peptone, the absence of which in Old Tuberculin he believed to be due to hydrolytic change by the tubercle bacillus. It should be noted that the tuberculous rabbits Califano used in his experiments had been infected with a slightly virulent human strain which produced mild chronic localized lesions, and as it will appear later, the dose of tuberculin used was relatively small, which leaves the question an open one.

Preobraschenski (5) studied the reaction of the ear-vessels of the tubercle-infected rabbit to tuberculin. He observed a vasodilator effect in the normal and an increased sensibility in early tuberculous infection. However, a bouillon concentrate produced similar effects which must be regarded as a nonspecific action. Perfusion of the ear-vessels of a tuberculous rabbit with epinephrine gave a vasoconstrictor response indistinguishable from that of the normal.

Working with the isolated intestine of the guinea pig, Maki (6) studied the action of various tubercle-bacillus derivatives upon the gut of normal and tuberculous animals, and he further compared the action of several autonomic drugs on the isolated intestine of normal and tuberculous guinea pigs. The results of his work indicated that the isolated intestine of the tuberculous guinea pig reacted to Old Tuberculin or to derivatives from the tubercle bacillus in no way differently from that of the normal animal. No hypersensitiveness of the isolated smooth muscle to products of the tubercle bacillus could be demonstrated.

Rondoni (7) likewise failed to observe a difference in the reaction to Old Tuberculin of the isolated heart of the tuberculous guinea pig as compared with that of the normal.

In the present work experiments were made to determine the action of tuberculin on the circulation of the normal and of the tuberculous animal, and to ascertain, if possible, the cause of the circulatory failure from tuberculin which supervenes some time after its injection. At the outset it should be emphasized that I do not urge the view that circulatory failure is indeed the cause of tuberculin death, but rather that the toxic manifestations of tuberculin, whether it be in the tuberculous or the normal animal, are characterized or at least associated with failing circulation and it seemed desirable to study this feature to some extent.

MATERIAL AND SCOPE

The tuberculin used in this work is a substance derived from a synthetic medium upon which the tubercle bacillus, human strain H37, was

permitted to grow. It is preparation 304-F to which reference was made in an earlier publication (3), in which its toxicity was studied in the guinea pig and rat, both normal and tubercle-infected. As pointed out there, this substance has all the characteristics of tuberculin, it is free from the nonspecific variable constituents present in the usual preparations of Old Tuberculin, and, if not a chemically pure substance, it is as nearly a pure tuberculin as can probably be had at this time. The experimental work described herein with the preparation 304-F concerns its action on the blood-pressure in the normal and tuberculous rabbit, the central and peripheral vasomotor responses during the progressive stages of tuberculin intoxication; the reaction of surviving blood-vessels of the normal and tuberculous guinea pig to the tuberculin in question; the reaction of these structures of tuberculous guinea pigs in severe tuberculin shock to certain drugs acting peripherally; and lastly, the comparative response of isolated smooth muscle of the tubercle-infected and coincidentally horse-serum sensitized guinea pig. The last was obviously designed to throw further light upon the question of identity or nonidentity of the tuberculin and the anaphylactic reactions.

Tubercle infection in the rabbit was produced, except when otherwise indicated, by an intravenous injection of 0.2 mgm. of a moderately virulent bovine strain, B-444, in which dose it produces diffuse pulmonary miliary tuberculosis, from which about 50 per cent of the animals die in from 20 to 30 days while those escaping the early effects die in from 60 to 180 days with advanced caseous and ulcerative lesions of the lungs and kidneys, and with the intestines, testicles and liver being involved in a considerable number of the cases. The guinea pigs were usually infected intraperitoneally with 0.1 mgm. H37 suspended in sterile saline solution. In some cases 0.25 mgm. of the bovine strain B-444 was similarly used.

THE TOXICITY OF 304-F IN RABBITS

Supplementing the experiments previously reported (3), the following data are presented to show the behavior and toxicity of the tuberculoprotein in nonanaesthetized tuberculous and normal rabbits. It will appear from table 1 that in the tuberculous rabbit as little as 5 mgm. per kilo, and probably less, is fatal, while the noninfected animal has survived a dose five times as great. When a toxic dose is given the symptoms in the noninfected rabbit are not unlike those in the infected animal. In from one-half to two hours following the injection there is some restlessness, hurried and somewhat labored respiration, progressive muscular weakness and collapse. Toward the end there may be clonic

convulsions which appear to be asphyxial. It will thus be seen that tuberculoprotein 304-F, which for all practical purposes is a highly concentrated and relatively pure tuberculin, exhibits a primary toxicity in the rabbit as in other mammalian species studied previously, and that the tuberculous rabbit is considerably more susceptible to it than the noninfected control.

THE ACTION OF 304-F ON THE CIRCULATION

These studies were made upon anaesthetized normal and tuberculous rabbits with a view to ascertaining the effects of the tuberculoprotein on

TABLE 1

Toxicity of 304-F in rabbits: intravenous injections

NUMBER OF EXERIMENT	WEIGHT	INFECTING DOSE OF B-444	DAYS AFTER INFECTION	DOSE OF TUBERCULOPROTEIN	RESULT
	kg.	*mgm.*		*mgm. per kilo*	
1	2.3	0.2	40	20	Symptoms within 2 hours and death in 6 hours
2	1.9	0.2	35	20	Symptoms within ½ hour and death in 2 hours
3	1.8	0.2	35	20	Symptoms within ½ hour and death in 6 hours
4	3.5	0.2	40	10	Symptoms within 2 hours and survived
5	1.9	0.2	38	10	Symptoms within 1½ hours; death within 18 hours
6	2.3	0.2	38	10	Symptoms within 2 hours; death within 18 hours
7	1.8	0.5	32	5	Symptoms within ½ hour; death within 1 hour
8	1.2	0.5	32	5	Symptoms within 1½ hours; death within 2 hours
9	2.2	0.2	80	5	Sick for 36 hours; survived
10	2.8	Control		75	Died within 18 hours; pulmonary haemorrhage
11	2.1	Control		50	Died within 18 hours; pulmonary haemorrhage
12	2.4	Control		35	Died within 18 hours; pulmonary haemorrhage
13	1.7	Control		35	Slight symptoms; survived
14	1.9	Control		25	Slight symptoms; survived
15	2.0	Control		25	Slight symptoms; survived
16	2.2	Control		25	No symptoms

the arterial pressure and the reactions of the vasomotor centre to certain stimuli following the injection of this substance.

The rabbits were anaesthetized for the most part with urethane and morphine subcutaneously, though in a few experiments paraldehyde was given orally. Usually 10 to 20 mgm. morphine sulphate per kilo and 0.5 to 1.0 gm. per kilo of urethane were injected hypodermically. When complete anaesthesia was secured, tracheotomy was performed and the usual arrangements were made for recording of the blood-pressure from

the left carotid artery. The right sciatic nerve and left depressor were dissected out, divided, and arranged for stimulation centrally. In this manner the blood-pressure curve was followed after the injection of the tuberculoprotein and the activity of the vasomotor centre ascertained from time to time by the blood-pressure response to central stimulation of the sciatic or depressor. In some of the experiments curare was given and artificial respiration was resorted to.

The results of these experiments may now be briefly described as follows: The immediate effect of the injection of tuberculoprotein in the normal or tuberculous animal is negligible. During the injection there may be a very slight and transient rise in blood-pressure such as might follow the intravenous injection of an equivalent volume of salt solution. After the immediate effects of the injection are over the blood-pressure mounts to a slightly higher level which may be maintained for about a half-hour or longer, this being followed by gradually declining blood pressure (see figure 1, a, b, c, d, and figure 2, a, b, c). Up to this point the effects in the tuberculous animal are not different from those of the normal. In a series of 6 normal rabbits, thus treated with 25 to 100 mgm. per kilo of tuberculoprotein the blood-pressure declined on an average of 25 per cent of the initial in a period varying from 65 minutes to three hours and a half. This reduced level of arterial blood-pressure, having been reached, was generally maintained, or it took on an upward trend, and stimulation of the central sciatic elicited a normal vasoconstrictor response, as did stimulation of the depressor bring about the usual fall in blood-pressure (figure 2, d, e). In the tuberculous animal the fall in blood-pressure, initiated some time after the injection of tuberculoprotein, takes on a more precipitous character, reaching a considerably lower level than that of the normal under similar circumstances, and, what is more significant, is the fact that stimulation of the central sciatic results in a greatly diminished pressor response which may ultimately be abolished completely. Similarly the reaction to stimulation of the depressor nerve is considerably reduced (figure 1, e, and figure 3, c, d). In a series of 12 experiments, in which 25 to 30 mgm. per kilo of tuberculoprotein were injected into tuberculous rabbits, the blood-pressure fell, on an average, about 55 per cent of the initial in from 30 minutes to two hours, at which time stimulation of the central sciatic either failed to elicit response or gave a much-reduced rise in blood-pressure as compared with the normal. Asphyxia likewise failed to elicit any reaction from the vasomotor centre (figure 1, g). On the other hand, drugs

acting peripherally produced normal responses. Thus an injection of pituitary in one instance, in which stimulation of the central sciatic was ineffective, raised the blood-pressure from 30 to 80 mm. Hg or nearly the normal level, and maintained it for about 20 minutes (figure 1, f). Likewise 0.1 mgm. epinephrine raised the blood-pressure from a little less than 30 mm. Hg to over 110, that is, considerably above the normal level at a time when stimulation of the central sciatic was entirely inef-

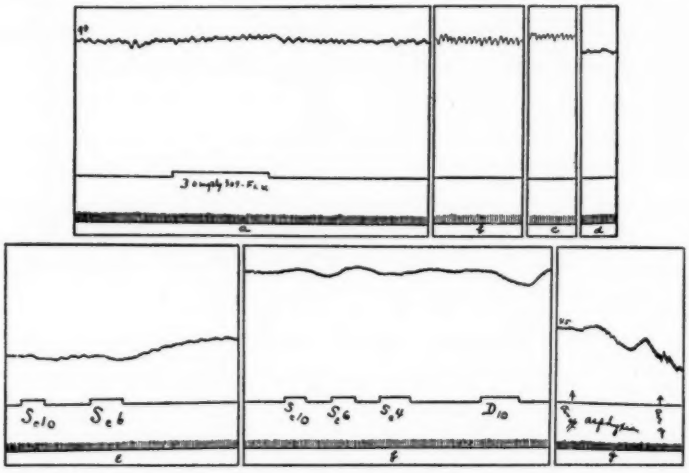

FIGURE 1

Rabbit, 1.7 kg., 0.5 mgm. B-444, i.v., 37 days. Urethane and morphine. Injected 30 mgm. per kilo 304-F, i.v., at a. Note slight augmentation in blood-pressure at b and c lasting 40 minutes. At d, one hour after injection, the blood-pressure began to decline. Two hours after injection the blood-pressure fell to 45 mm. Hg., as shown at e when stimulation of central sciatic is but slightly effective in producing reflex vasoconstriction. At f restoration of blood-pressure to normal level is shown following the injection of 1.5 mgm. per kilo of standard pituitary extract in 7 cc. per kilo of 5 per cent glucose. The effect is only temporary, however, and the centre fails to respond to stimulation of the central sciatic (Sc) and only slightly to stimulation of the depressor (D). The animal had been curarized and asphyxia at g fails to stimulate the vasomotor centre. Time in seconds.

fective (figure 3, d). It should be noted that the low blood-pressure *per se* does not seem the cause of the failure of the vasomotor centre to respond to central sciatic or depressor stimulation, for, when this is attempted when the blood-pressure is raised to a nearly normal level by means of pituitary or epinephrine, the result is no different, as shown in figure 1, f, and figure 3, d. It is obvious, therefore, that the pronounced action of tuberculoprotein on the circulation of the tubercle-infected

rabbit is a marked reduction in blood-pressure, which develops not immediately but after a considerable interval following its injection and that concomitantly with the fall in blood-pressure the vasomotor centre becomes increasingly insensitive to such stimuli which normally bring its action into play.

Further confirmatory evidence of the integrity of the peripheral vascular mechanism in tuberculin shock was obtained in a series of experiments upon guinea pigs in which perfusion of the surviving blood-vessels was carried out. The technique employed in these experiments was as follows: Under ether anaesthesia the skull was trephined, and with a stout probe the brain and spinal cord were destroyed. The thorax was split open and a cannula was inserted into the thoracic aorta. This was

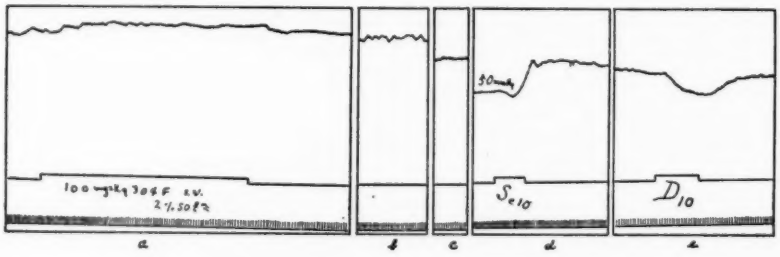

FIGURE 2

Normal rabbit. Urethane and morphine. At a injected 100 mgm. per kilo, 304-F, i.v. First fall in blood-pressure at c, 35 minutes after injection. At d, 2 hours and a half after injection, the blood-pressure fell from 85 to 50 mm. Hg., but stimulation of the central sciatic (Sc) and of the depressor (D) elicited good responses, indicating fair state of activity of the vasomotor centre.

connected by means of a three-way stop-cock with perfusion bottles containing oxygenated Ringer-Locke solution with 6 per cent gum arabic under constant pressure and maintained at constant temperature by a suitable heating device. The outflow cannula was placed in the inferior vena cava and the outflow rate recorded by means of the Condon tipper delivering a constant volume of about 3 cc. at each stroke. The emptying of the tipper was recorded on the smoked paper of a revolving kymograph by means of a signal magnet. In this manner the entire vascular system below the diaphragm was perfused.

The action of the tuberculoprotein on the calibre of the surviving blood-vessels was thus ascertained in normal, tuberculous, and tuberculin-shocked guinea pigs. The results of these experiments may be

best presented by referring to several representative tracings obtained under conditions described as follows:

A guinea pig, weighing 400 gm., had been inoculated 43 days pre-

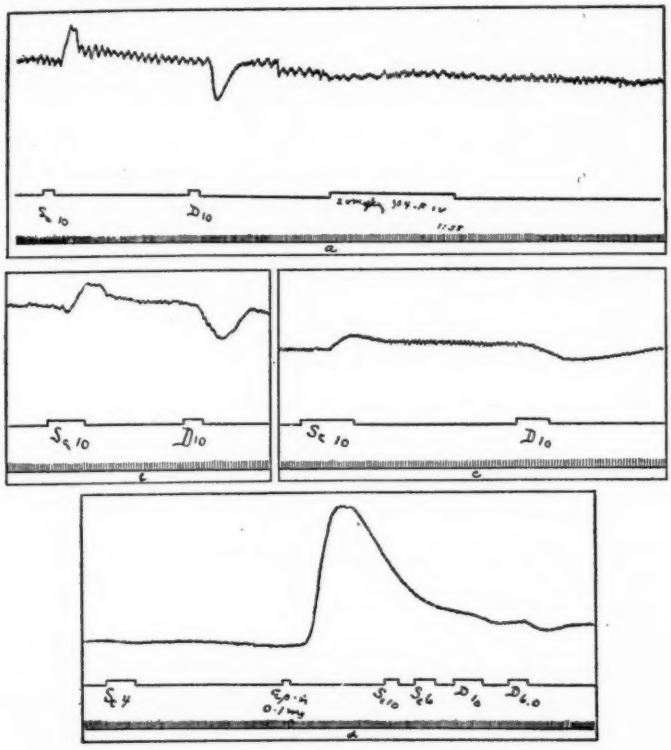

FIGURE 3

Rabbit, 1.6 kg., 0.5 mgm., B-444, i.v., 31 days. Morphine and urethane. Normal response to central sciatic and depressor stimulation followed by injection of 20 mgm. per kilo 304-F, i.v. At b, 20 minutes later, the blood-pressure had not yet begun to decline and stimulation of the central sciatic and of the depressor is effective. At c, 35 minutes after the injection, the blood-pressure began to decline and stimulation of the central sciatic is less effective, as is also the stimulation of the depressor nerve. One hour after the injection at d the blood-pressure had reached a low level, when stimulation of the central sciatic is no longer effective, while the response to epinephrine is normal. Afferent stimuli through the sciatic and depressor during the elevated blood-pressure are ineffective in arousing the vasomotor centre to greater activity.

viously with 0.25 mgm. bovine-strain (B-444) tubercle bacilli intraperitoneally. Blood-vessels were perfused, as described above, at a temperature of 37°C. and a constant pressure of 38 mm. Hg. Five

mgm. 304-F were injected into the arterial (inflow) cannula. No effect on the perfusion rate. Perfusion changed to a solution containing 1:50,000 epinephrine. Marked vasoconstriction resulted. Another injection of 5.0 mgm. 304-F into the arterial cannula had no effect upon the epinephrine vasoconstriction (figure 4).

A guinea pig, weighing 375 gm., had been similarly inoculated 23 days previously. Five mgm. 304-F were injected intravenously, giving rise to severe tuberculin shock that developed within two hours after the injection. Two and a half hours after the injection the animal was in grave condition and gave every appearance of supervening death. It was then quickly prepared in the usual manner and the surviving blood-vessels were perfused at 37°C. and 38 mm. Hg. Injection into the inflow cannula of epinephrine, pituitary extract, and acetyl choline gave the usual normal responses of vasoconstriction and vasodilation respectively.

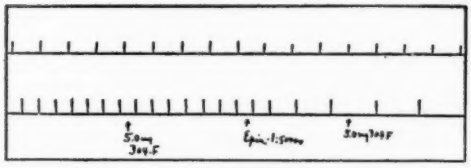

FIGURE 4

Guinea pig 400 gm. Infected with ¼ mgm. B-444 intraperitoneally 43 days. Pithed. Perfusion with Ringer-Locke-gum-arabic solution at 37°C. and 38 mm. Hg. Injection of 5.0 mgm. 304-F into the arterial cannula had no effect upon the calibre of the blood-vessels. Usual vasoconstriction followed the perfusion with 1:50,000 epinephrine, the rate being unaffected by the injection of 5.0 mgm. 304-F. Time in minutes.

This experiment clearly shows that tuberculin shock in its severest form does not damage the peripheral vascular mechanism and this is fully in harmony with the experiments previously described in the intact rabbit.

In the next experiment an attempt was made to compare the vascular reaction to tuberculoprotein and to horse-serum in an animal both sensitized to horse-serum and infected with the tubercle bacillus. A guinea pig, weighing 360 gm. had been infected intraperitoneally with 0.25 mgm. H37 thirty-six days previously, and was sensitized to horse-serum 10 days after infection by the injection of 0.1 cc. horse-serum intraperitoneally. The animal was prepared for perfusion in the usual manner, which was carried out at 37°C. and 40 mm. Hg. An injection into the inflow cannula of 5 mgm. 304-F was without effect. Later 0.5 cc. horse-serum was injected into the cannula and there was a slight and

transient increase in perfusion rate. Further injection of epinephrine, acetyl choline, and pituitary extract gave normal responses (figure 5, a, b). Without putting too much emphasis at this time upon the response of the surviving blood-vessels of the sensitized guinea pig to horse-serum, it is evident that the reaction to tuberculoprotein in the tubercle-infected animal need not be of the same type as that to the antigen to which the animal had been sensitized.

In summarizing the results of these experiments in conjunction with those carried out upon the rabbit it may be concluded that tuberculin is devoid of any peripheral action on the blood-vessels, that the peripheral structures of the vascular system are intact in tuberculin shock, but that the vasomotor center sustains irreparable damage in the sys-

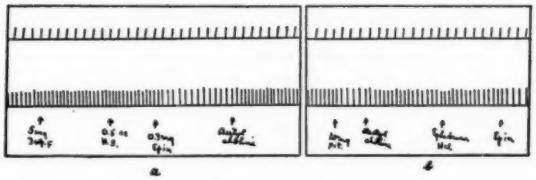

FIGURE 5

Guinea pig, 360 gm., infected with $\frac{1}{4}$ mgm. H37, thirty-six days, and sensitized with 0.1 cc. horse-serum 26 days, both intraperitoneally. Perfusion with Ringer-Locke-gum-arabic solution. Note the dissimilar response to 5.0 mgm. 304-F and to 0.5 cc. horse-serum injected into the arterial cannula. Note the normal subsequent reactions to epinephrine, acetyl choline and pituitary. Ephedrine had no effect.

temic action of tuberculin and that there is apparently no essential difference, except that of degree, in the systemic action of tuberculin in the tuberculous as compared with the normal animal.

FURTHER EVIDENCE OF THE NONIDENTITY OF TUBERCULIN SHOCK AND ANAPHYLACTIC SHOCK

In 1922 (8) the results of a series of experiments were reported which indicated that while anaphylactic sensitization to tuberculoprotein may occur in the susceptible guinea pig coincidently with tubercle infection, it was not an essential concomitant, and that the tuberculin skin reaction could not be considered as a manifestation of general protein hypersensitiveness, but rather of specific tubercle infection. Those experiments were carried out by the aid of the well-known anaphylactic response of the isolated uterus of sensitized guinea pigs to antigen. It was difficult to interpret some of the results with certainty because of the

nonspecific plain-muscle stimulating action of the usual commercial tuberculin, due no doubt to the presence therein of such nonspecific substances as histamine. With the relatively pure tuberculin now available it seemed desirable to repeat some of those experiments in order to differentiate further, if possible, between the tuberculin reaction and the response of protein-sensitized animals to the antigen.

In the rabbit sensitized to horse-serum the intravenous injection of antigen after an adequate incubation period produces a result quite different from that of the injection of tuberculoprotein in the tubercle-infected animals. Unlike the latter there is an immediate fall in blood-pressure following the injection of horse-serum in the sensitized rabbit, and an hour or more later, after the blood-pressure has reached its

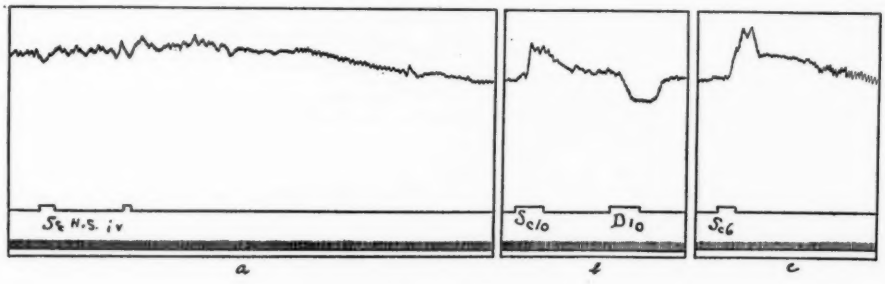

FIGURE 6

Rabbit sensitized with 2.0 cc. horse-serum intravenously 21 days. Urethane-morphine anaesthesia. Note immediate fall in blood-pressure following the intravenous injection of 5 cc. horse-serum. At b, one hour later, curare was injected under artificial respiration. Note normal reactions to central sciatic and central depressor stimulation. At c, 15 minutes later, note greater vasomotor response to stimulation of central sciatic with stronger current.

stationary low-level, central stimulation of the sciatic or depressor nerve elicits normal response showing the integrity of the vasomotor centre (see figure 6). In like manner isolated uteri of guinea pigs both infected with the tubercle bacillus and sensitized with horse-serum respond differently to tuberculoprotein and to horse-serum, the former having no effect and the latter giving a characteristic reaction with typical desensitization to further treatment with antigen (figures 7 & 8). These experiments confirm the earlier contention that tuberculin hypersensitiveness in the tuberculous animal is of a different order from that of anaphylactic hypersensitiveness resulting from sensitization to a foreign protein. It may further be reasserted that though general tuberculoprotein hypersensitization may develop in the tubercle-infected animal

it is not an essential concomitant of infection and not at all an essential factor in the tuberculin reaction, local or general. That anaphylactic hypersensitiveness to tuberculoprotein may also occur in the tuberculous animal became apparent from some experiments in which the comparative bronchoconstrictor action of tuberculoprotein and of horse-serum,

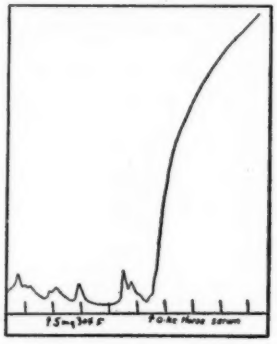

FIGURE 7

Guinea pig 440 gm. Infected with $\frac{1}{4}$ mgm. H37 twenty-seven days and sensitized with 0.1 cc. horse serum seventeen days, intraperitoneally. Isolated uterus suspended in oxygenated Ringer-Locke-solution at 38°C. Note lack of response to 5.0 mgm. 304-F and typical anaphylactic reaction to 0.1 cc. horse-serum. Time in minutes.

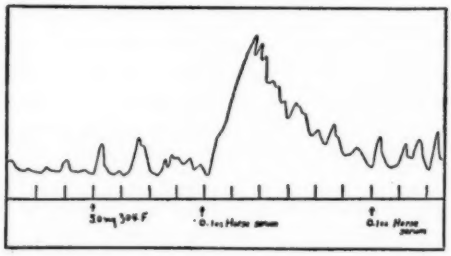

FIGURE 8

Guinea pig, 450 gm. Prepared as above. Negative response to 5.0 mgm. 304-F, typical anaphylactic reaction to 0.1 cc. horse-serum and desensitization to second dose of 0.1 cc. horse-serum.

as devised by Koessler and Lewis (9), was studied in guinea pigs infected with the tubercle bacillus and sensitized to horse-serum. The reaction is almost certainly obtained when horse-serum is injected intravenously in the sensitized guinea pigs (figure 9), which is identical with that following the intravenous injection of histamine in the normal animal. In the tubercle-infected guinea pig the intravenous injection of tuberculo-

protein is usually without effect (figure 10), though this is not the invariable rule, for an occasional positive reaction has at times been ob-

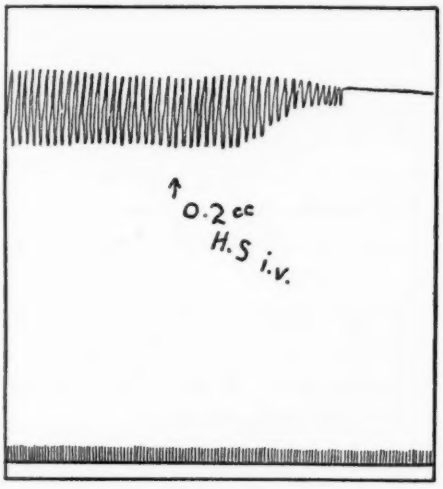

FIGURE 9

Guinea pig, 580 gm., sensitized with 0.1 cc. horse-serum intraperitoneally 16 days. Note almost immediate bronchospasm following the intravenous injection of 0.2 cc. horse-serum. Time in seconds.

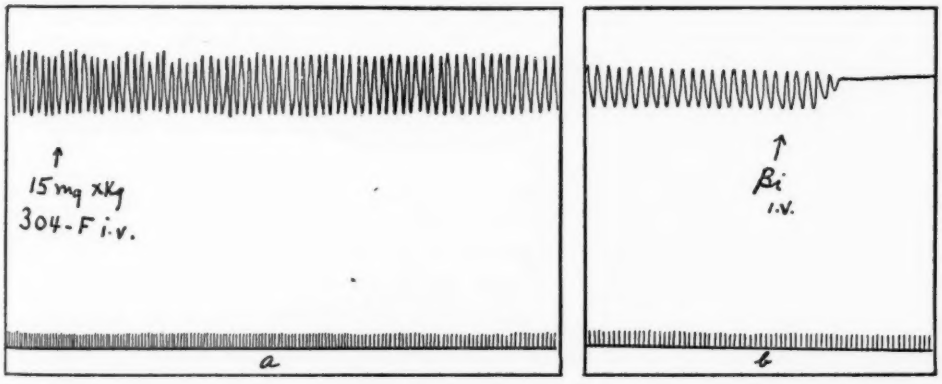

FIGURE 10

Guinea pig, 580 gm. Infected with 0.2 mgm. B-444 intraperitoneally 25 days. No bronchial constriction following the intravenous injection of 15 mgm. per kilo of 304-F. At b, 15 minutes later, histamine was injected intravenously with almost immediate typical reaction.

tained, suggesting that in the guinea pig at least general anaphylactic hypersensitiveness to tuberculoprotein may accompany the infection.

CONCLUSIONS

1. Tuberculoprotein has a primary toxicity in normal animals, but is many times more toxic in tubercle-infected animals.

2. Tuberculoprotein, injected intravenously into tuberculous rabbits under anaesthesia, produces a progressive decline in arterial blood-pressure and failing response of the vasomotor centre to afferent stimuli.

3. Tuberculoprotein is without apparent effect upon the surviving blood-vessels of normal or tuberculous guinea pigs. The surviving blood-vessels of the tubercle-infected guinea pig in severe tuberculin shock respond normally to drugs acting on the peripheral vascular mechanism.

4. Comparative tests of anaphylactic and tuberculin hypersensitiveness made upon animals, simultaneously infected with tubercle and sensitized to horse-serum, have shown that the two phenomena are distinct and independent of each other.

REFERENCES

(1) KIRCHHEIM AND TUCZEK: Arch. exp. Path. & Pharmak., 1914, lxxvii, 387.
(2) SEIBERT: Amer. Rev. Tub., 1928, xvii, 394.
(3) SMITH: U. S. Pub. Health Rep., 1928, xliii, 2817.
(4) CALIFANO: Zeit. ges. exp. Med., 1925, xlv, 484.
(5) PREOBRASCHENSKI: Ibid., 1925, xlv, 452.
(6) MAKI: Ibid., 1924, xliv, 143.
(7) RONDONI: Cited in Ber. über d. ges. Phys. & exp. Pharmak., 1923, xv, 387.
(8) SMITH: Jour. Med. Res., 1922, xliii, 435.
(9) KOESSLER AND LEWIS: Arch. Int. Med., 1927, xxxix, 163.
(10) LONG AND SEIBERT: Amer. Rev. Tuberc., 1926, xiii, 448 & 408.

BOOKS[1]

LAWRASON BROWN: *Rules for recovery from tuberculosis. Philadelphia, Pa., Lea & Febiger, 1934, ed. 6, pp. 275, cloth, $1.75.*

FRED G. HOLMES: *Tuberculosis. New York and London, D. Appleton-Century Company, 1935, pp. vii + 312, cloth, $2.00.*

By CHARLES W. MILLS

Many books on tuberculosis have been written for the patient. They are useful and necessary; "a necessary evil" some might say. One of the physician's hardest psychological problems is that of inducing a patient to follow directions without worrying too much about his insides. From this standpoint the ideal patient is the one who wishes only enough knowledge about his disease to enable him to follow the prescribed course toward recovery and to avoid mistakes, and whose usual thoughts are centered on things outside himself. Every physician will agree that the birds and the flowers are much preferable to the lights and the liver as objects of the patient's intellectual interest. The difficulty comes, of course, from the fact that it is almost impossible for anyone to view himself purely objectively. Especially when the question is

[1] THE REVIEW plans to carry a section devoted to *Book Reviews* from time to time. It accordingly invites contributions of this nature from any authors who may see fit to submit manuscripts and will be glad to accept those reviews that measure up to standards that would comprehend such features as thorough familiarity with the text of the work under review, as well as knowledge of the subject and field covered by the book; apposite comparisons with related texts; critical ability and treatment; good literary form; and helpful description of contents. Uncritical praise and repetition of publisher's "blurbs" will be as undesirable as savage or personal attacks; neither will be tolerated. The main—almost the sole—purpose of an acceptable review should be to inform and to entertain. No limits or restrictions will be set on length of manuscript or manner of treatment provided the above-mentioned general considerations are adhered to. All reviews must be submitted gratuitously and those accepted will be published without compensation. Manuscript should be prepared in standard form (typewritten, one side of sheet only, double-spaced, etc.), and according to the style set in the reviews printed above.

Any opinions expressed are to be considered as those of the reviewer alone, and the widest latitude consistent with probity, ordinary courtesy and fairness will be allowed in this respect. In no way are they to be regarded as representing opinions of the publisher or editors.

In general, reviews will appear under the reviewer's name, initials or pseudonym. If, however, good and sufficient reasons can be adduced, worthy anonymous or unsigned reviews may be published, provided the author's name is known to the editor.—*Editor.*

that of studying his own disease, thought must almost of necessity become subjective and carry with it a more or less harmful emotional tinge. Even the physician, trained as he is to view disease objectively, when he becomes a patient, is tarred with the same stick.

But the ideal patient, from this standpoint, is a *rara avis*. The subject uppermost in the average patient's mind, as the conversation at any sanatorium dinner-table will attest, is that bomb which has rudely burst within him and disrupted his whole life, that is to say his illness. He insists on, or more exactly, cannot help thinking about it, talking about it, and learning from every possible source all he can about it. Such being the case, the physician must willy-nilly submit, but it behooves him to do all he can to keep the sources pure. It is astounding what masses of misinformation about tuberculosis some patients can accumulate, and give credence to, from busy-body friends, barber-shop acquaintances, or newspaper advertisements. The physician, of course, tries his best to educate as well as to treat, but is often handicapped by lack of time in doing the job thoroughly. Books, such as the two under review, therefore, serve a very useful purpose as a source of correct information. Both of these particular books answer, in a simple and understandable way, the questions about tuberculosis which the patient is interested in and both are authoritative. Either of them can be unhesitatingly recommended to the patient, or to the layman interested in the subject, and the physician himself will find in them much useful information not in medical text-books.

Doctor Brown's book has become a classic in this field. The fact that it has now gone through six editions attests its popularity, a popularity well deserved. The subject matter is well chosen and presented in the author's usual clear and forceful style. New chapters on *Surgical Treatment*, on *Getting up after Bed-rest*, and on *Returning Home*, have been added to the previous editions.

Doctor Holmes's book is the newest entrant in this particular class. His is a longer book and of somewhat wider scope than Doctor Brown's, covering a large area of the field of tuberculosis, and touching on practically every point which can conceivably be of interest or importance to the nonmedical reader. Particularly good are the chapters on *Choice of a Physician*, on *Planning the Treatment*, and on *Patent Medicines*. The latter chapter is especially timely and might, if heeded, save the credulous advertisement reader or radio-listener many times the price of the book. There is a second section of the book dealing principally with collapse therapy and treating very thoroughly this department, which has come to be of such great importance.

The only adverse criticism of Doctor Holmes's book is a certain carelessness in writing. It gives evidence of having been too hastily put together and insufficiently revised. There are too many misused words and, from the stand-

point of syntax, poorly constructed sentences. For instance, the word "regime" is repeatedly used for regimen. "Equitable climate" is used for equable climate. "Case" instead of patient is another example. This latter, to be sure, is medical jargon, but is better avoided. Undoubtedly such rough spots will be smoothed in a second edition and this will add to the attractiveness of a very excellent book. The subject matter is well arranged, and the book is very readable and should prove popular.

T. E. HAMMOND: *The constitution and its reaction in health. H. K. Lewis & Co., Ltd., London, 1934, pp. ix + 160, cloth, 7s, 6d, net.*

By LOUIS B. BALDWIN

In this brief book the author attempts to show the importance of the constitutional factor in health and disease. He feels that in recent years there has been too great a break with tradition and people have forgotten how to live. "The result is too great a strain on the nervous system, and hence much of the ill health that prevails."

In his chapter on *Constitution*, the author divides people into two main classes,—the hyposthenic and hypersthenic, and in considerable detail contrasts the two. The former are pale, poorly built, lack "nerve energy" and are subject to chronic infections but, as a rule, easily overcome acute diseases. The latter, on the contrary, have good color, good physique, are inclined to be active and not subject to chronic disease but have poor resistance to acute infections. He goes on to point out the importance of many factors in the constitution which should be taken into consideration in the management of life and the treatment of disease. For instance, he maintains that although the sun is essential it may do harm even in moderate amounts in certain conditions and in certain individuals. It may deprive the hyposthenic of energy, and it may stimulate the hypersthenic too much. The sun is harmful to the aged, the cachectic and the sick. He says that those who live in regions where the sun is always shining are by no means robust nor have they a great resistance to infection. Several chapters attempt to formulate rules for habits of living, and point out how constitutional factors should always be taken into consideration.

He finally maps out briefly his treatment of the asthenic state and for the first time skirts the outer shell of scientific medicine, for he not only discusses the aetiology of asthenia but discusses its drug therapy.

The book as a whole gives some food for thought, for it cannot be denied that scientific medicine has fallen short so far from explaining the part that constitution plays in health and disease. But the author makes many statements which would be hard to prove on scientific grounds, and one is forced

to wonder whether his observations are not often merely a matter of dogmatic opinion rather than founded on sound facts.

MAX GERSON: *Diättherapie der Lungentuberkulose, with X-ray findings and a chapter by Dr. Felix Fleischner. Vienna, Austria, Franz Deuticke, 1934, 154 illustrations in the text, pp. xii + 619, paper, M. 36.*

By MAX PINNER

Dr. Gerson's thesis is fairly simple: tuberculosis is a constitutional disease; it therefore is necessary to change by adequate treatment the constitutional derangement. This can be done effectively by the proper diet, that is, the Gerson diet. The aim of this treatment is (1) to alleviate inflammation, which is achieved by his so-called antiallergic diet (exclusion of all capillary poisons, of table salt, of canned goods, of certain protein foods, of such foods that are empirically idiosyncratic to the individual patient); (2) to increase the elimination of toxins and products of degradation which is done by the administration of such materials that enhance elimination through bowels, bile, kidneys and skin and by the exclusion of drugs and foods that counteract elimination; (3) to provide materials for regenerative processes (mineral salts, vitamines, cholesterol, hormones); and (4) to maintain the metabolic balance by general hygienic measures and by properly balanced food.

This general scheme is the basis of the diet which seems to require from the physician a fairly encyclopaedic knowledge, a more than ordinary gift of divination and angelic patience, and from the patient a good deal of moral and, at times at least, intestinal fortitude in the literal sense of the word. The demands that this dietetic therapy makes on the physician are not overstated, because there is no Gerson diet that should be followed schematically in all patients and throughout the entire course of the disease; on the contrary, it must undergo infinite variations and modifications depending upon individual needs and on the phases of the morbid development. Its physiological catholicity—under proper management—is truly astounding, since it will, for example, act phlogistically or antiphlogistically.

Since, then, it is almost too much to expect that any physician can ever fully master the intricacy of this treatment, its efficiency must essentially be judged from Dr. Gerson's own results. He makes, in this book, an unusually thorough attempt to present the available evidence in the form of 51 detailed case-histories, amply documented by roentgenograms. The entire roentgenological material has been studied and reported by an impartial observer and eminent expert in his field, Dr. Felix Fleischner, Vienna. The first 25 cases were observed in the special diet department of the *Urban Krankenhaus* in Berlin under the clinical directorship of Professor Hermann Zondek. After having

undertaken their study, Professor Zondek and Dr. Gerson were relieved of their work, and their clinical experiment was terminated abruptly and prematurely. Consequently, the observation time of the patients of this group was only about one year, more or less. In the remaining 26 patients from Dr. Gerson's private practice, the observation period is not much longer in the majority of cases. For a final, or even a decided judgment, such observation periods are, of course, much too short, particularly since practically all patients were far advanced. Considering the apparent unfavorable or even desperate prognosis of most of these 51 patients, one cannot help agreeing with Drs. Gerson and Fleischner that the demonstrable degree of improvement is encouraging, and in some cases astonishing. The reviewer believes, however, that the mere decrease in the size of cavity tends to produce more than justified optimism in these—as in so many other observers. Many phthisiotherapists might be inclined to accept the incomplete evidence in favor of the Gerson diet and to give it a practical trial, were it not for Dr. Gerson's emphatic statement that patients under his treatment should not be submitted to other and better tried forms of therapy, such as collapse measures.

But this is not the only deterrent; there is, as mentioned, the baffling problem of its practical application. And there is the insecurity of its theoretical foundation. As said at the beginning of this review, Dr. Gerson's thesis is simple; but it is far from simple to extract it in intelligible form from a book of nearly 600 pages, from a verbose discussion that is often lost in innumerable ramifications, and from theoretical premises that seem strange, often arbitrary, even abstruse, and seldom proved. A reasonable understanding—the reviewer doubts that he has reached it—is further hindered by a curiously novel terminology. If a given subject requires new terms they should be created *ad hoc;* but the borrowing of such familiar words as allergy, disposition, idiosyncrasy and others, and introducing them with new connotations, that are only faintly reminiscent of their accepted meaning, must create confusion.

There is much of interest in this book; many significant topics are discussed that are not mentioned in this review; many keen observations are reported; and fascinating problems are formulated. But the difficulties mentioned will undoubtedly restrict the number of readers.

It seems desirable to this reviewer that a brief abstract (50 to 100 pages) be made from this work and that it be translated from *Gersonese* into a generally accepted language. It would be preferable to have such a treatise printed in the customary form and not like Dr. Gerson's original work in at least eight different types (not counting headings). Since this multiplicity of type appears not infrequently on a single page it produces a disquieting impression, not unlike a tabloid newspaper or an emphatically gesticulating orator playing on all the registers of the human voice.

Dr. Fleischner has contributed all roentgenological descriptions and interpretations and an essay of nearly 30 pages on the roentgenology of healing processes in pulmonary tuberculosis. The contribution of this author, who has much original work in this field to his credit, is a model for concise and elegant description and for reasoned and convincing interpretation.

HENRY C. SHERMAN: *Food and health. The Macmillan Company, New York, 1934, pp. x + 296, cloth, $2.50.*

By LOUIS B. BALDWIN

A great many advances have been made in the knowledge of food in recent years. Consequently, it is no longer believed that if the diet contains nothing more than an adequate amount of protein, carbohydrate and fat, nutrition and health will be satisfactorily maintained. In addition to the vitamines, several mineral elements are essential to the structure and functioning of the body. In this concise review of the subject of food and its relation to health, the author very clearly and simply describes the problems related to nutrition, and indicates how they can be met. He considers that the western races need a thorough understanding of the subject in order to maintain a proper state of health, while the primitive races achieve the same ends instinctively. For instance, in China, bone constitutes an important source of dietary calcium; ribs being broken up and cooked in sweetened vinegar. On analysis, a simple serving of such a dish has been found to supply as much calcium as the American estimate of a day's need.

The chapters on vitamines are brief but adequate. Here again a practical emphasis is placed on the natural sources of vitamines in the diet. In order to supplement the text with more detailed information, an appendix is added, in which are listed the caloric contents of common servings and commercial units of foods; foods as sources of protein and mineral elements; and foods as sources of vitamines. An appendix contains a fourth chapter dealing with illustrative records of actual meals, each of which is in accordance with the principles explained by the book. There is also an excellent selected bibliography.

The subject as a whole is well handled, and the book should prove to be a useful addition to the medical library, in spite of the fact that in its brevity it deals with the various subjects rather superficially. To an intelligent layman it will make interesting reading, and should go far to create a sound knowledge of food and its relation to health.

TH. NAEGELI AND H. SCHULTE-TIGGES: *Künstliche Zwerchfellähmung bei der Behandlung der Lungentuberkulose. Tuberkulose-Bibliothek, edited by Lydia*

Rabinowitsch, No. 54, pp. 61 with 49 illustrations, Johann Ambrosius Barth, Leipzig, 1935, paper, Mk. 7.40.

By MAX PINNER

In the brief space of 38 pages the authors present a concise and adequate, though naturally not exhaustive, discussion of phrenic-nerve interruption in the treatment of pulmonary tuberculosis. The six chapters deal with the anatomy of the phrenic nerve, respiratory mechanism, operative technique, accidents and complications, indications and causes and prevention of failures. This monograph is more an objective review of the subject than an expression of an individual opinion. The authors excel in conciseness, and they have packed an unusual amount of information and pertinent data in the few pages of their text. There is an extensive and—rather rare in recent German medical books—quite an international bibliography. In addition to the text, there are 17 pages of unusually clear illustrations, all of them, with the exception of one, roentgenograms, accompanied by brief clinical notes. All cases chosen show good, and in a number of cases exceptionally good, results. However, the text deals adequately with failures, limitations and operative accidents. The impression is gained that the authors are far from being faddists and over-enthusiastic, but incline rather toward the conservative side.

This monograph is one of the well-known publications *Tuberkulose-Bibliothek*, which were started in 1921 by Doctor Lydia Rabinowitsch, as supplements to the *Zeitschrift für Tuberkulose*. Since the AMERICAN REVIEW OF TUBERCULOSIS has not previously published a review of any of the preceding monographs in this series, it seems pertinent to this review to point out how important has been the editorial work of Doctor Rabinowitsch, who acted as Editor, for both the *Zeitschrift* and for the *Tuberkulose Bibliothek* until the spring of 1933. This is the last monograph of this series edited by Doctor Rabinowitsch, apparently a delayed manuscript, since numbers 55 and 56 have already appeared under another editorship.

The series of the *Tuberkulose Bibliothek* to date includes a wide field of subjects of interest to the tuberculosis worker. It is a monument to the able editorship of Doctor Rabinowitsch. She has been wise and discriminating in the accumulation and selection of the material; and has thus been, at least indirectly, a potent influence on the development of tuberculosis work. But more, she has helped and inspired many a young worker and she has always been ready, with patience and with a fine gentleness, freely to give advice and assistance from the broad background of her experience and knowledge. These are only a few and necessarily inadequate remarks about Doctor Rabinowitsch, the editor; but, unfortunately, this is not the place to write about Doctor Rabinowitsch, the scientist.

T. E. HAMMOND: *Principles in the treatment of inflammation. London, England, H. K. Lewis & Co., Ltd., 1934, pp. x + 210, cloth, 10s, 6d.*

By MAX PINNER

Most experienced physicians feel, in their less official and more pensive moods, some disappointment in view of the discrepancy between the rapid accumulation of specialized knowledge in bacteriology, immunology, biochemistry and surgical technique on the one hand, and the annoyingly slow growth in therapeusis and genuine explanation on the other. The latter, although the final aim of scientific pursuit, reaches so often hardly beyond the level of an inarticulate wish or a vague dream because of the failure to realize that the formulation of the problem constitutes a limitation of the answer and the method of investigation determines the particular facet of the problem that, with the help of good luck and ingenuity, might be elucidated. The failure to recognize such obvious and fundamental principles, more often than actual inavailability of knowledge, is the cause for iconoclastic dissatisfaction with the present state of affairs and for attempts, such as Dr. Hammond's, to discard or disregard recently established knowledge in order to delve into the more comfortable prescientific past. But it seems a rather unfair procedure to compare the achievements of the wisdom and logic of a few select individuals with the work of the average man of to-day; in other words, to compare exquisite wisdom and perspicacity of past centuries with routine laboratory and clinical methods of the present.

Dr. Hammond's plea for the return to the clinical wisdom of Sir James Paget should, it seems, be coupled with the plea for a thorough digestion and integration of the more recent accumulations of facts by minds that are of the calibre of the greatest of bygone generations, but not with the advice to disregard modern knowledge, because it has not yet been applied in its full potentialities to clinical medicine.

It seems aberrant, therefore, to revive *diatheses* and *dyscrasias*, albeit in new terminological disguises, as long as no greater clarity and precision is added to the concepts. It does not seem justified to discuss, and quite vaguely at that, drugs with the actions of *alterantia*, of disthenics or of euthenics. It is questionable progress to assert that chronic infections are caused by ill health and not *vice versa*, in the absence of any information of what ill health is beyond indefinite statement of constitutional derangements and depressed vitality.

However, in the premises of the book there is much that will strike a sympathetic chord in many a reader: the emphasis on clinical observation, the plea to treat and understand the patient rather than the disease, and to judge therapeutic results not in the postoperative period but in later years, the suggestion for a more determined use of pain-relieving measures. But, as a

whole, the book conveys too much nineteenth-century atmosphere: pleasant and intense, but prescientific and limited.

FELICE COVA: *Semeiotica polmonare ragionata. Bologna, L. Cappelli, 1934, with 20 tables and 65 figures, pp. 328, liras 35.*

By GEORGE WEBER

It is to be regretted that difficulties of language prevent the medical profession from getting better acquainted with the work done by the Italian phthisiologists, especially in the postwar period.

After Parodi's excellent book on artificial pneumothorax, we have now this new work of Felice Cova, a former pupil of Forlanini. He dedicates his treatise to students and young doctors, but the scholarly thoroughness with which he pursues his subject makes it obviously more suitable for the specialist. In spite of the enormous progress of the laboratory and of the X-ray, Cova firmly believes "that the examination of the patient, at least in the field of thoracic diseases, is still pre-eminent," and this may be considered an attempt to resist the tendency of recent years to depend overmuch on paraclinical methods in the making of a diagnosis.

The book is divided into two parts: *General* and *Special Semeiology*. In the first part, which is preceded by a summary of the anatomy and conformation of the chest, the types of respiration, etc., the four stages of a physical examination, namely, inspection, palpation, percussion and auscultation, are minutely dissected, and each sign, normal and abnormal, is considered. To be sure, we find in most text-books the directions for a good technique and a brief explanation of the conditions in which the different phenomena are produced, but the author is not satisfied with that. From Hippocrates, through Auenbrugger and Laennec to Skoda and Pottenger, he reviews and analyzes all the theories, and then draws the conclusions, trying to give for each phenomenon an explanation corresponding to definite physical laws.

Of course, a detailed review of the book is impossible in a short space due to the nature of the subject, which, although not new, is made interesting by some of Cova's original observations; as, for instance, one in the first section, about the presence of the anterior lobule, and its disappearance as a first symptom of apical lesions. Another chapter especially worthy of note is that about the muscular spasm over the seat of the lesion first demonstrated by Pottenger in 1910 and explained by him as a reflex stimulation of the motor nerves. Cova considers the symptom of great value, having found it himself in 73 per cent of recent cases and in 62 per cent of chronic cases.

The second part deals with the symptoms and signs of the different pathological conditions; and so we have a chapter on pneumonia, one on pleurisy,

pneumothorax, pulmonary abscess, etc., with a last chapter describing the cough and its mechanics. The author's experience in thoracoscopy gives him opportunity to treat at length the physiopathology of the pleural cavity, and especially convincing is the explanation he gives concerning the formation of some of the so-called sacculated effusions. In a normal pleural cavity, with a lung of normal elasticity, the negative pressure should be even. However, besides elasticity, the lung has a certain weight. While, in the upper half this weight increases the lung's tendency to contract toward the hilum, in the lower half the contraction is partly neutralized by this same weight. The result of this disparity of tension is that the negative pressure is higher in the upper half and increases toward the apex. Therefore, a small and a slow forming effusion is apt to be kept in place by a process of "suction," especially if it occurs at the level of a parenchymal lesion, which always increases the tension of the lung "*in situ*." Furthermore, Cova suggests that these slight effusions, by organizing, may be, in most of the cases, responsible for pleural adhesions, especially in the apical dome.

The fine art of physical examination and direct observation of the patient seems to be slowly lapsing into disregard, and Cova is to be praised for trying to keep it alive. While the necessity and importance of the X-ray cannot, nowadays, be denied, on the other hand, is it not going too far when we read of a physical examination performed only after a radiograph or the fluoroscope has shown pulmonary lesions? How many times does the country physician and even the specialist upon consultation, for lack of a portable machine, have to depend for his diagnosis only on the signs that his more or less experienced senses are able to detect, and his knowledge of pulmonary mechanics able to explain?

The work may appear too detailed and heavy, and in places lacking lucidity, despite the effort to be clear even at the cost of repetition. This is due to the fact that physics, and especially acoustics, occupy a predominant part in the book, but this is more or less unavoidable considering the nature and the purpose of the subject. On the whole, however, it is highly interesting, and, being complete, it has a distinct value.

Brief Comment

M. FLESCH-THEBESIUS: *Chirurgische Tuberkulose, with an introduction by V. Schmieden. Theodor Steinkopff, Dresden and Leipzig, 1933, with 58 illustrations, pp. xv + 194, paper, RM. 15.*

This textbook on surgical tuberculosis is addressed to the general practitioner. The author has achieved, in a remarkable degree, to combine lucidity with conciseness and to select those facts from the wide field of his subject that the practitioner needs to know to diagnose, and treat intelligently, tuberculosis of

the bones and joints. His discussion on heliotherapy should be pointed out in particular, for its soundness, both in regard to the simplicity and accuracy of the fundamental physical and physiological factors and in regard to its well balanced clinical appraisal. Another chapter of outstanding value is an analysis of the respective merits of conservative and surgical treatment with well-defined indications for either mode of therapy. Most of the illustrations are instructive and clearly reproduced roentgenograms.

ROBERT WOLLHEIM AND WALTER H. SCHAUINSLAND: *The Herrmannsdorfer-Sauerbruch Diet, with a foreword by Joseph Alexander. Professional Scientific Service, New York, 1935, pp. 64, paper, $1.00.*

A brief outline of the dietary regimen which is apparently quite effective in cutaneous tuberculosis, but whose value in other localizations is still much *sub judice.* In the foreword we read: "In the present booklet we seek to present to the American medical profession a dispassionate outline of the theoretical foundations and general principles of the Herrmannsdorfer-Sauerbruch Diet, together with full directions for its practical application." After reading the book, "the theoretical foundations and general principles" remain as mysterious and questionable as they ever were. The practical application is clearly presented and the prescribed dietary is considerably better adapted to American markets and palates than were former German instructions. Even so, this diet still remains a man-sized job for physician, cook and patient.

ROBERT WOLLHEIM AND WALTER H. SCHAUINSLAND: *The equilibrated salt diet (Keining and Hopf), with a foreword by Charles R. Rein. New York City, Professional Scientific Service, 1934, pp. 64, paper, $1.50.*

An outline of a new dietary regimen whose "chief objective . . . . is to bring about relative predominance of potassium, calcium and magnesium cations over sodium cations in the body in order to restore the disturbed cation relation to normal." This diet is recommended particularly for skin diseases.

G. SANDOR: *Contribution à l'étude des antigènes des microbes pathogènes. Paris, France, G. Doin et Cie, 1935, pp. iv + 140, paper, 25 fr.*

A monographic study of the physico-chemical behavior of bacterial antigens, based chiefly on work with tubercle bacillus antigens. The main theoretical thesis is the demonstration of "the convergence of the physical characters" of diastases and antigens of pathogenic bacteria, so that the two groups of substances seem "to play biological rôles of the same order."

Asthma bronchiale, Supplement to Immunität, Allergie und Infektions-Krankheiten. Ärztliche Rundschau, Otto Gmelin, Munich, 1933, iv, nos. 4–6, pp. 136, paper.

This is a collection of the following brief papers: *Robert Herbst:* The anatomical and pathologico-physiological foundations of bronchial asthma; *H. Gudehus:* Vegetative and endocrine systems and bronchial asthma; *Wilhelm Krohn:* Allergic asthma; *Otto Wiese:* Bronchial asthma in childhood; *Georg Schröder:* Bronchial asthma and tuberculosis; *K. Hansen:* Differential diagnosis of bronchial asthma; *E. Gräfe:* Internal (medicinal, dietary, pyretic) and radiation treatment of bronchial asthma; *Ludwig Hofbauer:* Respiratory treatment of bronchial asthma; *J. H. Schultz:* Psychological treatment of bronchial asthma; *J. van Niekerk:* The allergen-free and the specifically desensitizing treatment of bronchial asthma; *Erich Hesse:* A critical analysis of the operative treatment of bronchial asthma. Most of these papers are brief, more or less critical, reviews of the recent literature, and with or without the addition of the author's own experience or observations. Some of the papers (for instance, Gudehus, Schultz) are entirely original contributions. As a whole this little monograph will probably well fulfill its apparent purpose, that is, to present in easily digestible form the more significant facts and theories elaborated during the last 10 or 20 years concerning this disease. Even the strictly therapeutic chapters do not add much real optimism to the general gloomy therapeutic attitude. Most of the papers include brief but definitely useful bibliographies.

C. E. SCHUNTERMANN: *Lungenentzündung, Supplement to Immunität, Allergie und Infektionskrankheiten. Ärztliche Rundschau, Otto Gmelin, Munich, 1933, iv, nos. 1–3, pp. 140, with 38 figs., paper, RM. 7.50.*

This is a monograph which utilizes "a critical analysis of the literature and numerous clinical observations and scientific observations" of the author, "it must therefore—have a subjective character." It is a concise, well-organized and practical presentation of the subject. The pathological, bacteriological and immunological features are discussed in an easily understandable manner without the distortions that such attempts at "popularization" so frequently engender. The emphasis is definitely on the clinical aspects. We miss a chapter on the pathophysiology of pneumonia. Serum-therapy is treated slightly and inadequately, apparently on account of the lack of the author's experience with this form of treatment. This study will undoubtedly be of interest to readers who wish to get acquainted with the general management of patients with lobar pneumonia as practised in Germany.

BEULAH WELDON BURHOE: *The social adjustment of the tuberculous, with a preface by Kendall Emerson. New York, National Tuberculosis Association, 1934, pp. 55, paper.*

In no human disease is the recognition of its social character more essential than in the instance of tuberculosis. It differs from most other communicable

diseases in its protracted course. Once infected with the tubercle bacillus, the human body may become a prolonged social, as well as medical problem. The recognition of the equal importance of these two aspects of the disease has long existed. Treatment of its medical phase, however, has far outstripped attention to its equally significant social aspect. For three years past, the National Tuberculosis Association has encouraged closer study of the social problems which tuberculosis produces. Mrs. Burhoe as the Association's Rehabilitation Secretary has prepared this pamphlet on the Social Adjustment of the Tuberculous as the fruit of careful research and experimentation in this field. The conclusions reached are not definitive but in its presentation of trends it constitutes a valuable contribution to the already considerable literature on the welfare aspects of tuberculosis. (*From the Preface by Kendall Emerson, M.D.*)

KYUSAKU OGINO: *Conception period of women: English translation by Yonez Miyagawa. Harrisburg, Pa., Medical Arts Publishing Company, 1934, pp. 94, paper.*

As long as the phthisiotherapist believes that pregnancy is contraindicated in some tuberculous women, he will be faced with appeals for advice as to contraceptive methods, unless he choses to subject his patients to the psychological trauma of complete sexual abstinence. Although the notion that fertilization is possible only during a restricted interval of the female's sexual cycle, is as old as history, only of late has modern endocrinological research and adequate statistical investigation lent credence to this belief. The prevention of conception, if possible, by periodic abstinence from sexual activity, would seem *a priori* a most suitable method for those to whom other perhaps as yet more reliable procedures would be abhorrent for various reasons. It is simple to carry out and relatively free from physiological or psychological trauma and furthermore has received sanction by members of the Catholic clergy. Undoubtedly the infallibility of the method is still open to question, but regarding this point the reader must judge for himself. In this pamphlet present available knowledge is well summarized and semi-popularly presented, so that it may serve equally well as a summary for the physician who does not care to consult the original literature *in extenso*, as well as a manual of instruction for the patient. The author, by whose name the method is sometimes called, adheres closely to a factual presentation and judiciously avoids all controversial issues of social approval or disapproval in regard to prevenception. Moreover, as he wisely points out in his introduction, the information contained might also be utilized by those who have been relatively infertile and are anxious to bear children.

Books Received

SEDER, RUTH ABELSON: The costs of tuberculosis with special reference to the adequacy of medical care and treatment. New York, National Tuberculosis Association, 1934, pp. 35, paper.

CURTI, AGOSTINO: Le Lobiti Tisiogene. Milano, Tipografia Enrico Zerboni (published for Ospedale Sanatoriale), 1935, pp. 136 with 58 illustrations, paper, price L. 35.

The Romance of Exploration and Emergency First-Aid from Stanley to Byrd. New York, Burroughs Wellcome & Co., 1935, pp. 95, cloth.

POSTWAR CHANGES IN THE TREND OF TUBERCULOSIS MORTALITY

J. H. WATKINS[1]

Soon after the World War and the accompanying influenza epidemic a fundamental change in the trend of tuberculosis mortality became recognizable. Mortality records subsequent to 1900 reveal a gradual decrease in the tuberculosis death-rate until the war years, when a rise occurred, followed in 1919 and 1920 by a sharp decline. As annual mortality data accumulated it became apparent that the effect of the war, or rather of those agencies acting upon the tuberculosis mortality rate during the period of conflict, was manifested in different ways among different populations. Chart 1, for example, shows the course of mortality for a comparable period of years, in the United States (Expanding Registration Area), in England and Wales, and in Scotland. A logarithmic scale has been used in order to emphasize the rates of decline.

For the Registration Area of the United States, a period (1900–1916) of fairly even decline was interrupted by a rise in mortality in 1917 and 1918 followed by a rapid decline until 1921, after which another period of uniform but less rapid downward trend began and has since continued. The last-named period, however, differs from the prewar one in that (1) the 1921 rate was definitely lower than might have been expected if the prewar decline had been resumed, and (2) the rate of subsequent decline was considerably greater (3.74 per cent annually) than in the earlier years (2.38 per cent annually). For England and Wales, however, this picture is not duplicated. After the rise in 1914–1918 and the subsequent decline to 1921, the trend of tuberculosis mortality which existed prior to the war was rather precisely resumed. No drop in the position of the trend-line occurred; nor is the postwar trend (2.67 per cent annually) significantly different from that for 1900–1914 (2.54 per cent annually). *A priori*, one would expect the trend of mortality for Scotland to follow closely that of England and Wales. Such, however, is not the case. The course of the curve for Scotland is quite similar to that for the United States.

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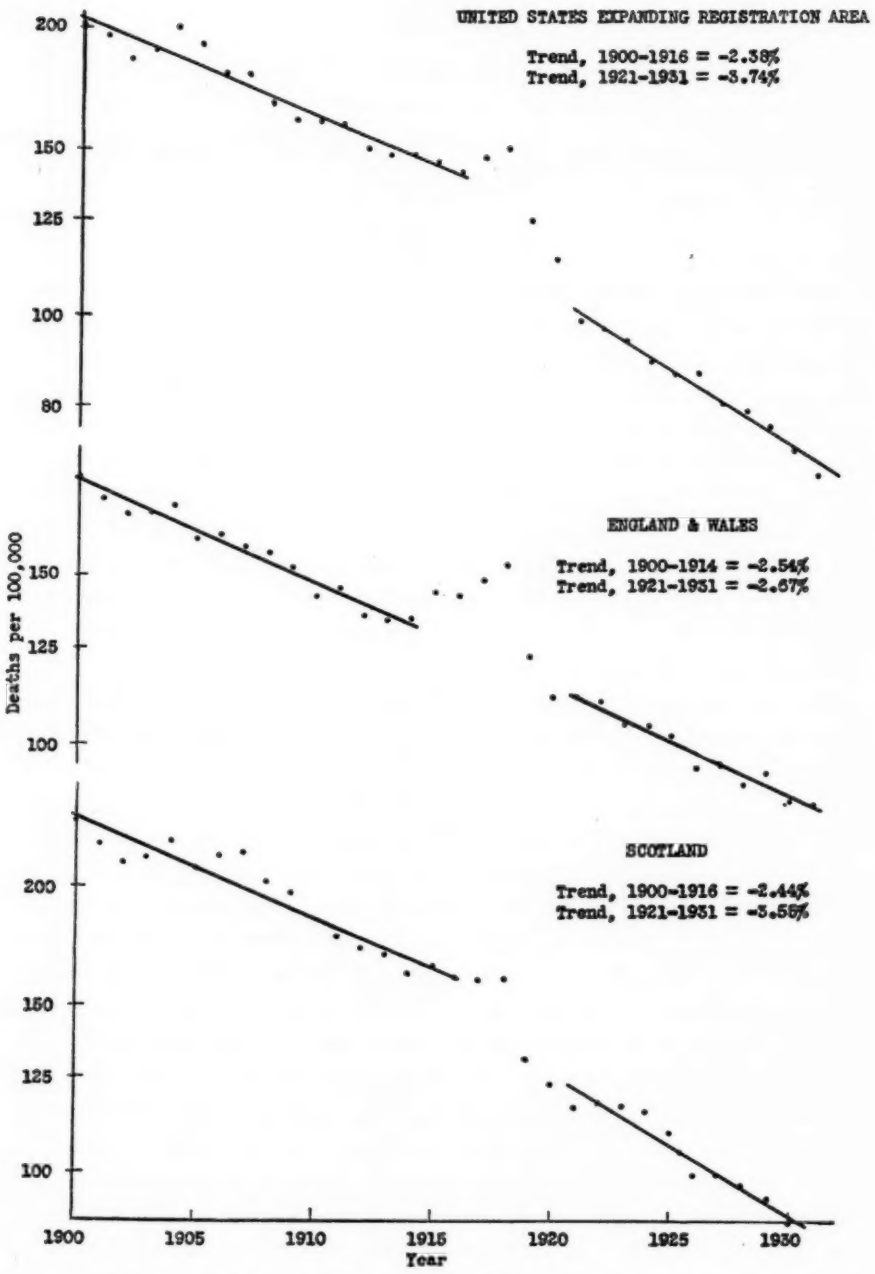

CHART 1. Trends of tuberculosis (all forms) mortality in the United States, England and Wales, and Scotland since 1900.

It is the purpose of the present study to describe the trend of mortality from tuberculosis in the United States previous to and subsequent to the period of the World War and the years immediately following it. An acceleration in the decline of tuberculosis is an important phenomenon to note. Its extent and degree, in so far as shown by existing state data of mortality from all forms of tuberculosis and determined by an accurate fitting of logarithmic trend-lines, have not generally been studied, which is surprising enough in view of the great amount of attention which has been paid to the decline in the mortality rate of tuberculosis. Data for the states as units have been utilized, as well as age- and sex-rates for the U. S. Registration Area of 1900.

THE LITERATURE

The excellent statistical studies of tuberculosis mortality published by DePorte, Dublin, Drolet, Gray and Winslow, Krause, Sydenstricker, Whitney and others are well known, and need not be reviewed here, except as pertaining to the actual trends of the disease.

Britten and Sydenstricker (1), in 1923, following the increased mortality from pulmonary tuberculosis during 1915–1918, noted the greatest decline in the year 1921, which was the last year of their observation. This was marked enough to indicate an unusual deviation from the preceding trend line. The suggestion was made that the year 1921 might possibly be a point in the "trough" of a periodic wave, the crest of which was in the year 1918, and that later years might show an arrest in the decline if not an actual increase. Needless to say, no such arrest or increase has so far occurred.

Krause (2), 1926, showed that in the eighteen years before and including 1918 the mortality rate of tuberculosis declined approximately 25 per cent, and in the seven years after 1918 approximately 41 per cent. If the rate for the registration area in 1900 had continued for the United States as a whole, the excess of deaths from tuberculosis over what was estimated to have occurred would have been 33,500 annually for the first eighteen years and 110,000 for the last seven years (1918–1925 inclusive). He concluded that this post-war increase in lives "saved" was only in part due to the influenza epidemic of 1918, which operated in conjunction with sanatorium development, improved social and economic conditions, and the influence of the antituberculosis movement to further the decline in tuberculosis mortality.

A detailed graphic study of tuberculosis in Cleveland, including comparable data from Baltimore, was published by Green (3) in 1927. Cleveland showed no downward prewar trend but between 1918 and 1926 a decline in the tuberculosis mortality rate occurred. By sex- and age-groups, the postwar decline appeared more pronounced among the males than the females between the

ages of 15 and 40. For the age-group, 40–44, a definite positive or upward trend was experienced among the males. For Baltimore, a similar postwar decline was demonstrated not only among the males, but also for the females between the ages 15 and 40. As in Cleveland, the trend of mortality among males of the next higher age-group (40–44) was upward.

The most comprehensive study of trends in tuberculosis mortality which has come to the writer's attention was that of Lee (4) in 1929. As basic data, Lee used mortality rates of tuberculosis in Massachusetts for the years 1865 or 1887 to 1927, subdivided according to age, sex, and form of tuberculosis. Plotting logarithmic trend-lines, he showed that the downward trend of the postwar tuberculosis death rate has been markedly accelerated. This appears to be largely due to an increasing reduction in the male pulmonary tuberculosis rate for the wage-earning age-groups, 15–60 years. For age groups 15–19 and 20–29 the decrease in mortality was less rapid than prior to the war, although the opposite was true for ages 30–39. From an analysis of the trends of the rate for each month Lee reached the same conclusion as Krause, namely, that the decline was but little influenced by the influenza epidemic of 1918.

As regards trends of tuberculosis mortality in relation to sex, Putnam's (5) extensive analysis throws considerable light on the subject. The author studied deaths from pulmonary tuberculosis, by age-groups in the registration area of 1900 for the years 1870, 1880, 1890, 1900, 1910 and 1920, using the ratio of male to female deaths. In addition to a decline in tuberculosis prevalence at every age-group for both sexes during the 50-year period, the findings showed that the rate of decline was essentially the same for males and females at ages under 35, but at older ages the decline in female mortality was more rapid than that of the male. The author concluded that the determining factor in this sex difference at older age periods was the environmental strain, imposed more heavily upon males than females.

Sydenstricker (6), in 1929, using the 1926 data of DePorte (7), selected as a rural area the twelve New York counties in which the differences between the recorded and resident rate were less than 15 per cent, and computed annual rural mortality rates from tuberculosis for the years 1900 to 1926. For comparison, estimated annual urban rates for the same period were calculated by adding the computed excess of recorded rural deaths to the recorded urban mortality. Comparison of the two trend-lines indicated that "the net effect of the interplay of various factors upon the tuberculosis death-rate in urban and rural situations was approximately the same during the period from 1900 until the World War, but since then the forces favoring a decline have been somewhat more powerful in cities than in country districts."

THE PRESENT STUDY

State mortality rates: The death-rates from all forms of tuberculosis of the twenty-two states admitted to the Death Registration Area pre-

vious to 1912 were selected for study. These rates are easily available, and the use of state data overcomes, in large measure, discrepancies due to nonresident sanatorium deaths. By limiting the study to the states admitted before 1912, a varying number of years is available for evaluations of the prewar period. No figures for years before 1900 were used, although for several these are available. The writer agrees with Dublin (8) that 1900 "was the first year for reliable statistics on tuberculosis for any large part of the United States." The maximum number of years previous to 1917 utilized was then seventeen for the ten states, Massachusetts, New Jersey, Connecticut, New Hampshire, New York, Rhode Island, Vermont, Maine, Michigan and Indiana. California, Colorado, Maryland and Pennsylvania were admitted to the registration area in 1906, thus giving eleven prewar years for use. Washington and Wisconsin, admitted in 1908, had nine years, Ohio (1909) eight years, Minnesota, Montana and Utah (1910) seven years, and Kentucky and Missouri (1911) 6 years. Figures for the white population only were used for Maryland and Kentucky. United States Bureau of the Census figures were utilized for the years up to and including 1930, the rates being used where they were clearly computed from intercensus population estimates. Where these were not available, arithmetical estimates were made and rates computed. Deaths for 1931 were kindly supplied by state health officers directly or through the National Tuberculosis Association. Rates for New York State up to 1931 were copied from the *New York State Department of Health Report* for 1930, and that for 1931 from the *New York State Health News* of February 15, 1932. Annual tuberculosis mortality rates for twenty-one states were thus available, beginning at least with the year 1911 and ending with 1931.[2]

Age and sex rates: Mortality data for all forms of tuberculosis by age and sex for the Registration Area of 1900 were furnished by the Bureau of the Census and the National Tuberculosis Association. Rates were calculated from these, using arithmetic population estimates. The years included were 1900–1931, inclusive.

A serious question at once arises as to the validity of trend-lines based on as few as six determinations. An unduly large or small rate for a single year will have an effect relatively much greater when total observations are small than when they are numerous. Harmon (9) has demonstrated the wide variability in the trend of measles cases when based

[2] It did not seem desirable to include years later than 1931 because of the altered situation in the country due to the depression.

upon different spans of years. However, tuberculosis deaths by no means fluctuate as widely from year to year as do cases of measles. Chance variations among annual rates depend in magnitude chiefly upon the size of the population concerned. Of the twenty-one states only six had less than one million inhabitants in 1910, four of which, Maine, Vermont, New Hampshire, and Rhode Island, have seventeen prewar years available for study. The remaining two, Montana and Utah, have but seven prewar years for use, and hence trend lines based upon these must be open to suspicion. Because, then, of the relatively small chance deviations to be encountered in data of states with more than one million inhabitants, the author feels that, with the exception of Montana and Utah, at least an indication of the immediate prewar trend of tuberculosis can be established.

As mentioned above, the last year of the prewar period selected for study was 1916, and the first year of the postwar period was 1921. These are apparently consistent periods, although Britten and Sydenstricker (1) have noted the end of the prewar period as 1914. In five states, Massachusetts, Michigan, Pennsylvania, Maryland and Rhode Island, an inspection of the plotted rates shows that the end of the prewar decline was in 1914 or 1915. In the remaining seventeen the decline did not end before 1917. Study of the data also shows that 1921 was consistently the beginning of the postwar period of decline after recession from the high level of 1918.

Straight lines were fitted to the charted logarithms of the rates by the method described by R. A. Fisher (10). The slopes of these lines indicate the rapidity with which the rates were declining. A quantitative value for the slope or trend is readily given by the vertical fall of the line per unit of time, in this case one year.

Logarithms were used in order to determine the annual *rate* of decline. The trend of an arithmetic line (one fitted to the rates) would have given an estimate of the annual absolute decline, and would have been affected in part by the values of the rates themselves. For example, an arithmetic trend of 4, fitted to rates the mean of which was 160, would appear larger than an arithmetic trend of 3 fitted to rates having a mean of 80. The former, however, would mean an annual rate of decline of only 2.5 per cent, the latter, of 3.8 per cent. Logarithmic trends, on the other hand, give an accurate estimation of the actual *rates* of decline, irrespective of the absolute values of the rates to which the trend lines are fitted.

Differences between the prewar and postwar trends were tested for significance by the method outlined by Fisher (10).

Although the value of the trend in each case is a logarithm, these are expressed as annual percentage declines, and differences between them as differences in the annual percentage decline.

RESULTS

The trends for each state, prewar and postwar, are presented in table 1. For convenience, the states have been arranged in geographical divisions, the exceptions from the usual classification being the inclusion of Maryland (white) with New York, New Jersey and Pennsylvania as an "Atlantic" group, and Kentucky (white) with those states usually classed as "East North Central" to form an "East Central" group. The trend values which are statistically significant have been italicized. In chart 2 are shown trend lines represented by the trends of table 1, together with the annual rates to which the lines are fitted.

Trends of state rates: The prewar trend-lines of all states but four show a negative and significant rate of decline varying from −1.16 per cent annually for Michigan to −4.04, −3.09 and −3.03 per cent annually for Colorado, the white population of Kentucky, and Ohio, respectively. Two states, Montana and Utah, have positive or increasing trends of 2.16 and 2.09 per cent, respectively, both of which are statistically insignificant. As mentioned above, the small population of these states, and the small number of prewar years (seven) used throw further doubt upon the reliability of these trends as indices of the prewar rate of decline of tuberculosis. Also, Willcox (11) has recently presented evidence to indicate a serious defect in reporting in these states. The negative trends of Minnesota and Missouri, −1.61 and −1.14 per cent, respectively, are statistically insignificant, possibly due to the fact that but six years were available for computation. Although no clear-cut differences between the states as geographical groups appear to exist, it can be said that, in general, for the prewar period the New England states possess the greatest rates of decrease, only Connecticut having a rate of decline less than two per cent.

For the postwar period (column 2) the rate of decline has increased for every state but one (Vermont), varying from −1.28 for Montana to −6.02 per cent for Connecticut. Here again large trend values are not confined to any particular group of states; for five out of the six New Eng-

land states, however, an annual decrease occurred of more than 4 per cent. Little correlation appears to exist between the value of the two trends, prewar and postwar. For example, New Hampshire has a pre-

TABLE 1

Tuberculosis mortality trends for states expressed as annual per cent decline
Prewar period: 1911–1916
Postwar period: 1921–1931

	PREWAR	POSTWAR	DIFFERENCE
New England			
Maine	−2.52	−4.73	2.21
New Hampshire	−2.47	−5.52	3.05
Vermont	−2.67	−1.96	−0.71
Massachusetts	−2.57	−4.92	2.35
Rhode Island	−2.27	−5.17	2.90
Connecticut	−1.66	−6.02	4.36
Atlantic			
New York	−1.69	−4.20	2.51
New Jersey	−1.87	−3.65	1.78
Pennsylvania	−1.58	−4.83	3.25
Maryland (white)	−1.18	−4.68	3.50
East Central			
Ohio	−3.03	−3.74	0.71
Indiana	−1.91	−3.84	1.93
Michigan	−1.16	−1.97	0.81
Wisconsin	−2.18	−4.07	1.89
Kentucky (white)	−3.09	−3.64	0.55
West North Central			
Minnesota	−1.61	−5.89	4.28
Missouri	−1.14	−3.00	1.86
Mountain			
Montana	+2.16	−1.28	3.44
Colorado	−4.04	−5.59	1.55
Utah	+2.09	−5.62	7.71
Pacific			
Washington	−1.18	−3.35	2.17
California	−1.85	−4.92	3.07

war trend of −2.47 per cent, a decline comparatively rapid for that period; the postwar trend is also rapid, −5.52 per cent. The adjacent state of Vermont, however, has a prewar trend of −2.67 per cent and a

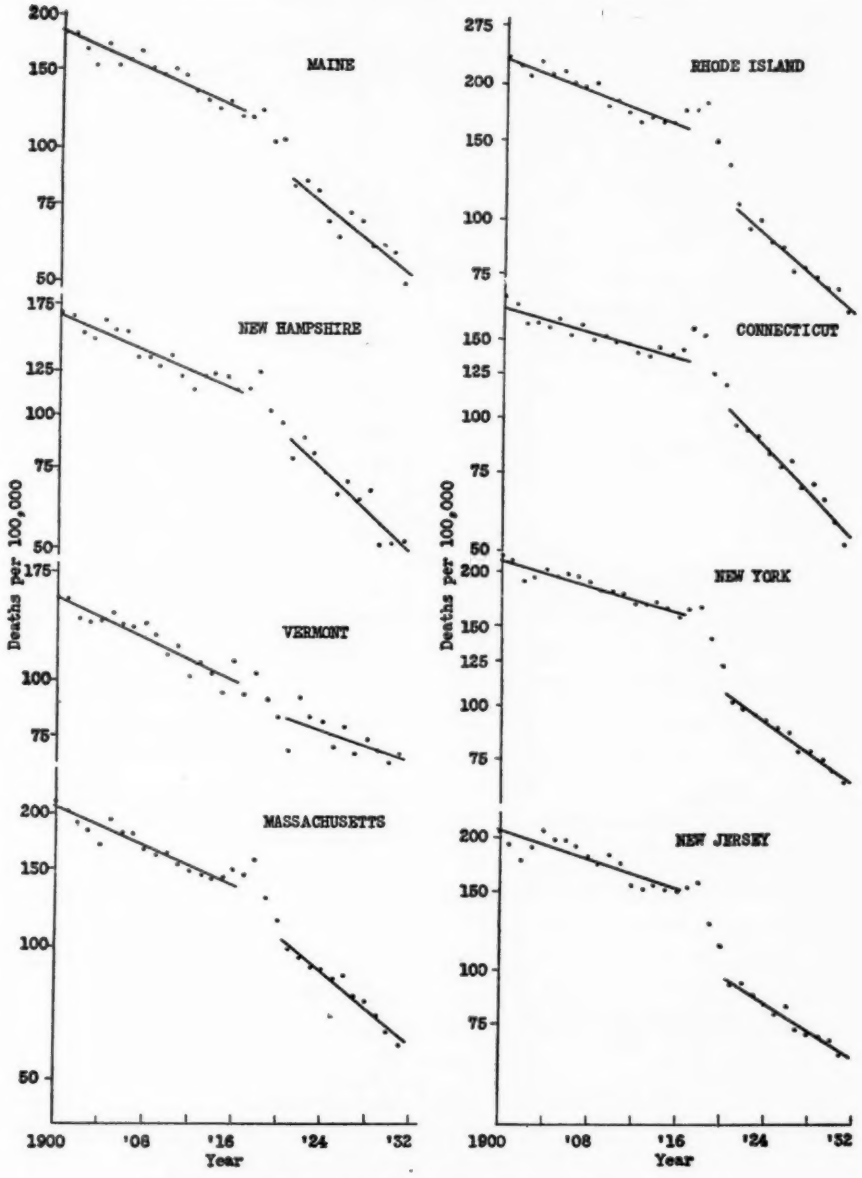

CHART 2. Trend of tuberculosis (all forms) mortality by states

postwar one of −1.96. That the rank of states by postwar rates of decline is not the same as for the period before the war is shown by the values for Connecticut and Minnesota. These states had relatively low

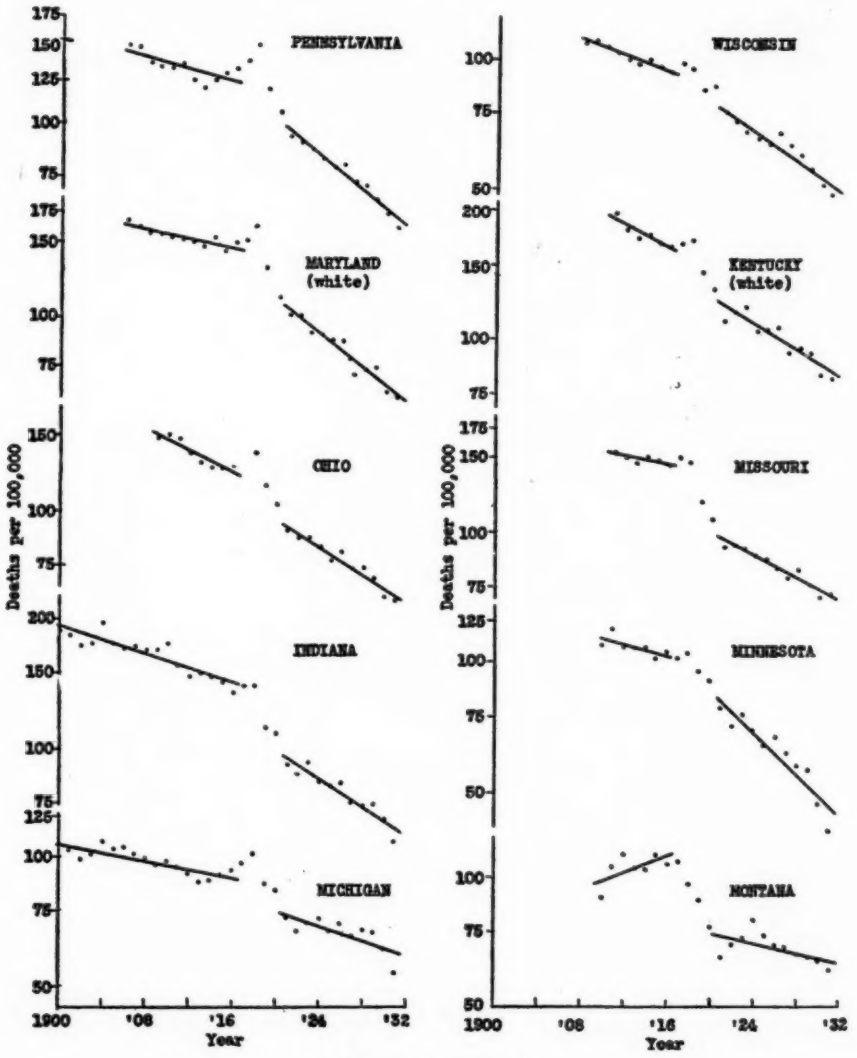

CHART 2 (*Continued*)

prewar trends of −1.66 and −1.61 per cent, and relatively high postwar trends of −6.02 and −5.89, respectively.

For detailed comparison of the later trend with that of prewar years, the differences between the two are also given in the last column of the table. Here a positive difference (prewar trend minus postwar trend) indicates a more rapid decline in the postwar period; and, conversely, a negative value indicates that annual rates after 1921 were not decreasing

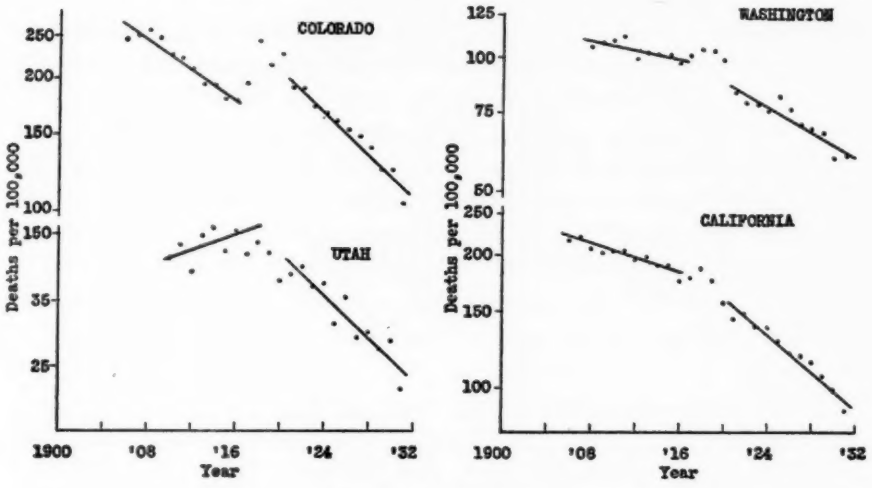

CHART 2 (*Concluded*)

as rapidly as before the war (1916). Those differences which are statistically significant have been italicized. With the exception of Vermont all states show an increased rate of decline in the later period, and for eighteen states this increase is statistically significant. The increase in the rates of decline was largest for Utah, 7.71, Connecticut, 4.36, and Minnesota, 4.28. In the case of Utah and Montana large and significant differences are due to the fact that an upward or positive prewar trend had turned to a negative trend after 1921, the differences being the sum of the two trends.

Increases in the rate of decline approach in size or are greater than the trends of the prewar period for all groups of states except those of the East Central group. Here significant differences were found only for Indiana and Wisconsin, these being less than 2 per cent. But aside from this observation no relation appears to exist between geographical position and the rate of decrease in tuberculosis.

In addition to an actual rate of decline-change between the two periods, another phenomenon is to be noted in many of the curves, namely, that the point at which the postwar trends began was much lower than would have been the case had the prewar trend continued after the war. This is true of the curves for Maine, Massachusetts, Rhode Island, New York, New Jersey, Maryland (white), Ohio, Indiana, Michigan, Kentucky (white), Missouri and Montana. With the exception of Colorado, curves of the other ten states appear as though a break in the trend had

occurred sometime during the war years, with no lowering of the general level of the postwar trend. For Colorado, the postwar trend-line, while steeper than the prewar one, began at a definitely higher level.

In order to obtain average trend values for geographical areas, the deaths from tuberculosis for the states within a division were added together, annual rates calculated for them, and the logs of these fitted with trend-lines as before. The years used were 1910–1916 inclusive, for the prewar period (except for the West North Central group, which was 1911–1916) and 1921–1931 for the postwar period. The trends and differences for these state groups are given in table 2 and are shown geographically in chart 3.

For all groups significant trends were obtained for prewar and postwar periods. The largest trends in the prewar period were those of the East Central and Mountain states, the latter group being greatly affected by the decline in Colorado, and the proportionally small numbers of Utah and Montana. In the postwar period, the rapid decline on the eastern seaboard is evident.

Turning to the differences between prewar and postwar trends given in the same table, significant postwar increases in the rate of decline of the tuberculosis mortality rate appear for all groups of states but the East Central one. New England and the Atlantic states show the largest differences between trends, with the Pacific and West North Central states following in order.

Trends of age and sex rates: Tuberculosis mortality curves by sex- and broad age-groups for the Registration States of 1900, together with the fitted prewar and postwar trend-lines are shown in chart 4. The values of the trends are given in table 3. For the males of all ages, the prewar trend was slight, −0.95 per cent, but the postwar trend was considerable, −3.51 per cent. The prewar all-age trend for females was greater than for the males, −2.90 per cent, and still greater, −4.45, during the postwar period. It is apparent that in general the downward trend exists throughout the life span for both sexes. A significant and negative annual percentage decline is shown for all age groups of both sexes, except for males, prewar, ages 1–4.9 and 45–64.9 in which the trends, though negative (−0.51 and −0.14 respectively), are slight and not statistically significant.

In order to compare the trends of different age groups during the two periods, chart 5 has been constructed with age as an abscissa, the ordinate being simply the corresponding value of the trend lines of chart 4 plotted

on a reversed scale. The height of a curve above the base line thus indicates the rapidity of the rate of decline at that age period.

TABLE 2

Tuberculosis mortality trends for groups of states

Prewar: 1910–1916

Postwar: 1921–1931

STATE GROUP	NUMBER OF STATES INCLUDED	PREWAR TREND	POSTWAR TREND	DIFFERENCE
New England	6	*−1.60*	*−4.95*	*3.35*
Atlantic	4	*−1.39*	*−4.24*	*2.85*
East Central	5	*−2.27*	*−3.34*	1.07
West North Central	2	*−1.67*	*−3.81*	*2.14*
Mountain	3	*−2.90*	*−4.74*	*1.84*
Pacific	2	*−2.04*	*−4.37*	*2.33*

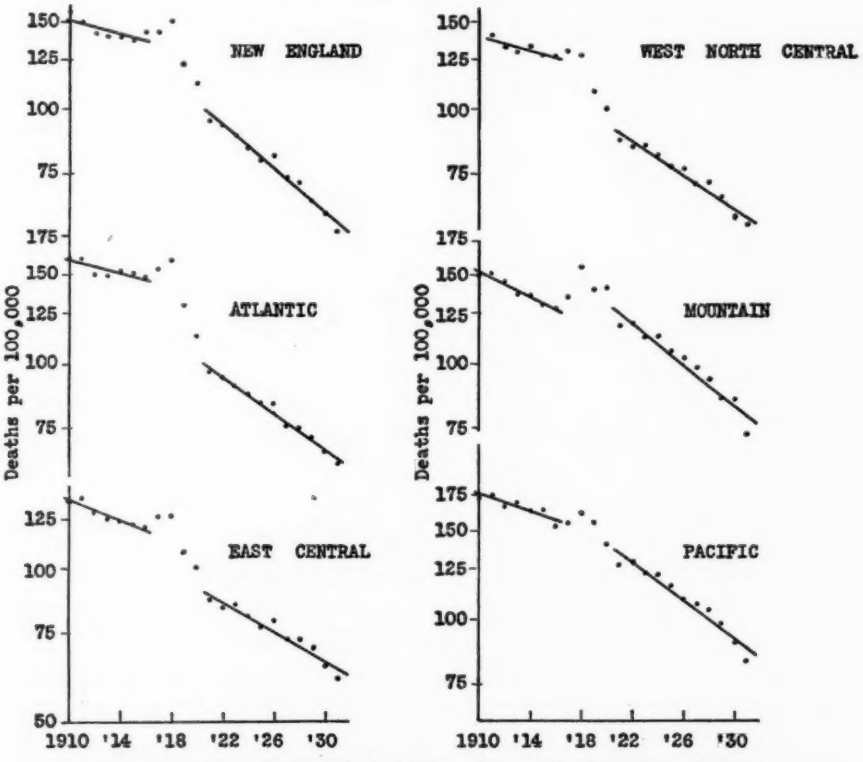

CHART 3. Trend of tuberculosis (all forms) mortality by groups of states

For the male curve during the prewar period, the rate of decline was greatest at the two extremes of life in the under-one age-group

(−2.83) and at ages over 65 years (−2.61). During childhood the trend was slight, but an increase was shown for the 15–24 age-group. With the exception of the two extremes, the decline (−1.60) was fastest in this

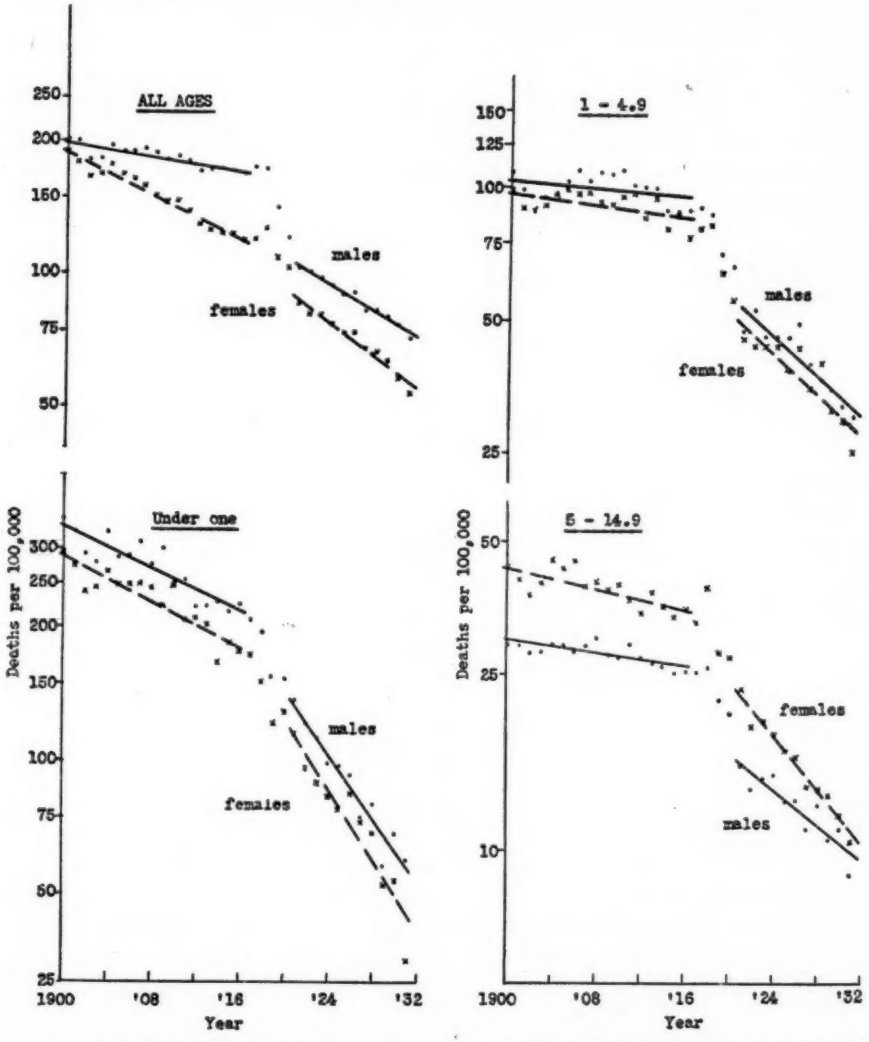

CHART 4. Trend of tuberculosis mortality by age and sex in the Registration States of 1900. 1900–1931.

period of early youth. The curve of postwar male trends, with the exception of the over 65 age-group, was considerably higher than the prewar curve, indicating that the downward trend of tuberculosis had tre-

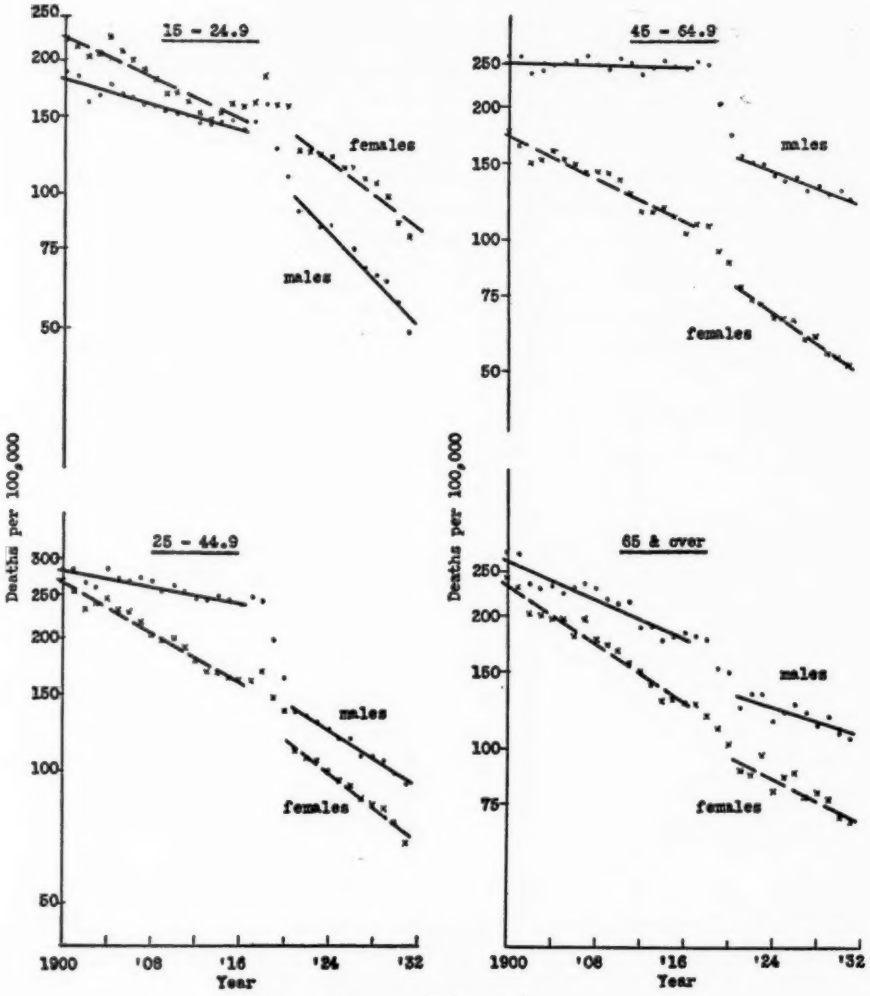

CHART 4 (*Concluded*)

mendously accelerated for all ages except the oldest which had suffered a decreased rate of decline.

The male column of differences in table 3 shows the greatest change occurring in the infant age-group, with smaller but still relatively large changes up to 25 years of age. For the older periods of life the trend differences gradually decrease until we find, in the over-65 group, a negative though statistically insignificant difference.

The prewar female trend curve differs from the corresponding male

curve in that after the minimum trend of the 1–4.9 age-group the trend increase extends to the 25–44.9 age-group, and drops only slightly at 45–54.9, before rising to a peak of −3.94 in the oldest age-group. The

TABLE 3

Trends in tuberculosis mortality by age and sex. U. S. Death Registration States of 1900
(Trends expressed as annual percentage decline)
Prewar: 1900–1916
Postwar: 1921–1931

AGE-GROUP	MALES		FEMALES		DIFFERENCES	
	Prewar	Postwar	Prewar	Postwar	Males	Females
All ages	−0.95	−3.51	−2.90	−4.45	2.56	1.55
Under 1	−2.83	−8.72	−2.94	−9.75	5.89	6.81
1– 4.9	−0.51	−5.27	−0.81	−5.44	4.76	4.63
5–14.9	−0.86	−4.81	−1.39	−7.33	3.95	5.94
15–24.9	−1.60	−6.12	−2.75	−4.42	4.52	1.67
25–44.9	−1.04	−3.75	−3.25	−4.59	2.71	1.34
45–64.9	−0.14	−2.19	−2.90	−4.04	2.05	1.14
65 and over	−2.61	−1.81	−3.94	−2.92	−0.80	−1.02

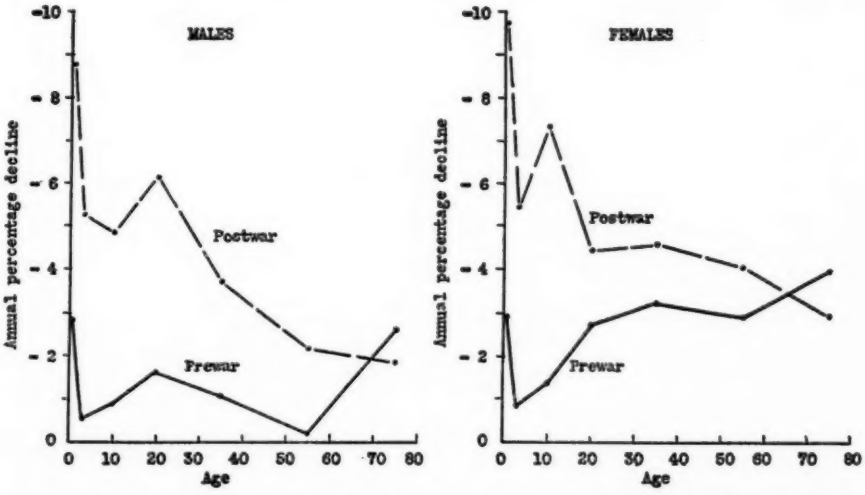

CHART 5. Tuberculosis mortality trend by age groups, U. S. Death Registration States of 1900.

high rates of decline at the older ages account for the great difference in the all-age female trend over that of the males. Turning to the postwar trends we find that, with the exception of the over-65 age-group, these are

considerably higher than the prewar trends. The secondary peak occurs here, however, in the 5–14.9 age-group instead of at 15–24.9 as in the male curve.

As with the males, differences between prewar and postwar trends (table 3) are greatest during infancy, but the large differences between trends occur only through 15 years of age. The difference at 15–24.9, −1.67, is only about one-fourth that of the previous age-group, and not greatly different from those at the older ages. The 65-and-over trend difference is again negative but insignificant, indicating the insufficiency of the data to distinguish between no change and an actual decrease in the downward trends of the rates.

Comparing males with females, the trends for both periods are, with one exception, greater for the latter. The exception is for the postwar

TABLE 4

Trend differences by sex

AGE-GROUP	PREWAR	POSTWAR
All ages	*1.95*	*0.94*
Under 1	0.11	1.03
1– 4.9	0.30	0.17
5–14.9	0.53	*2.52*
15–24.9	*1.15*	*−1.70*
25–44.9	*2.21*	*0.84*
45–64.9	*2.76*	*1.85*
65 and over	*1.33*	1.11

age-group, 15–24.9, in which the male trend was −6.12 per cent annually, and the female trend, −4.42, a difference statistically significant. During the prewar period sex differences in trends are slight and statistically insignificant for the age-periods under 15. Over this age they are larger and significant (table 4). The postwar sex difference at all ages is, though slight and barely significant, in favor of the females. Under 5 years of age the differences are insignificant but, until the highest age-group, are significant for the remaining ages.

With respect to the drop in the level of the postwar trends, shown by some of the state curves, a similar phenomenon is found in all but one or two of the male curves of chart 4, and clearly for but one of the female curves, that of the age group 1–4.9. For the male set of curves, the drop is large for all ages but the infant and over 65 years.

DISCUSSION

The fact that tuberculosis mortality has declined throughout the United States is again emphasized in the foregoing tables and charts. However, distinct differences in the rapidity or rate of decline are shown to exist in both periods, 1900–1916 and 1921–1931, among the 22 registration states of 1911. In general, the annual percentage rate of decline for the prewar period was greatest in New England, the exceptions being on the one hand, Connecticut, which showed a comparatively low rate of decline, and on the other, the states of Ohio, Kentucky (white) and Colorado with rapid decreases. After the war the situation became changed. The New England states, except for Vermont, still showed high rates of decline, but this feature of tuberculosis mortality was also quite generally true of the other states.

The phenomenon discussed in the opening paragraph of this paper, that the postwar was more rapid than the prewar decline of tuberculosis in the expanding registration area, is also true of the individual states, in most of which the rate of decline had doubled. The outstanding exception is Vermont, the postwar decline for which was actually proceeding at a slower rate than the prewar, although the difference is not statistically significant.

The situation respecting tuberculosis mortality in Vermont suggests that the blame for the failure of this state's postwar trend to deviate from that of the prewar trend in a manner comparable to the other states may perhaps be placed upon the industrial hazard involved in the granite industry. The mortality from tuberculosis among the granite-workers of that state is extemely high, as illustrated by the following figures, taken from *U. S. Public Health Service Bulletin no. 187* (12). The data are average annual death-rates per 100,000 from tuberculosis among granite-cutters in Barre, Vermont.

1900–1904	430
1905–1909	750
1910–1914	1080
1915–1919	1040
1920–1925	1470
1924–1926	1950

The importance of this increasing trend of tuberculosis mortality among granite-workers in the trend of the state rates is brought out by com-

paring pulmonary tuberculosis deaths among granite-cutters to those of the state as a whole. The following data are compiled from the *U. S. Mortality Statistics* and from table 68 of F. L. Hoffman's *The Problem of Dust Phthisis in the Granite-Stone Industry* (13).

	Deaths from pulmonary tuberculosis in Vermont	*Deaths from pulmonary tuberculosis among Vermont granite-cutters*	
		No.	*Per cent of state deaths*
1900–1904	2149	38	1.8
1905–1909	1942	105	5.4
1910–1914	1573	137	8.7
1915–1918[3]	1108	133	12.0

Industrial tuberculosis among the workers in the granite-stone industry appears, then, to be becoming an increasing factor in the rate-trend of the state as a whole.

The granite-stone industry, as shown by the *U.S. Bureau of the Census* (15) *Report on Mines and Quarries*, 1929, is chiefly confined to five states besides Vermont, only three of which, Massachusetts, Minnesota and Maine, are concerned in this study. The number of workers employed in the industry in Massachusetts and Minnesota is too small compared to the population as a whole to affect the total tuberculosis-mortality rates of the states. In Maine the wage-earners of this industry (881) are not greatly less than those of Vermont (952), while the 1929 populations of the two states were 795,000 and 359,000 respectively. That, in Maine also, tuberculosis mortality among granite workers in part determines the trend for the state is suggested by the fact that Maine ranks next to Vermont in having the lowest prewar-postwar trend difference among the New England group.

Of the remaining three states, trends for the two periods of which do not statistically differ, the prewar decline in two, Ohio and Kentucky (white) was already quite rapid. It has been previously pointed out by Gray (14) in 1928 that states with high death-rates from tuberculosis at the beginning of the period (1900–1924) studied by her were those with greatest subsequent decreases. Taking state-groups as a whole, the lowest prewar-postwar trend difference was found in the East Central states, the group ranking second in rapidity of prewar decline. The

[3] First nine months of 1918.

trends for groups of states indicate that the greatest trend differences occur in New England and along the two coasts.

Study of the tuberculosis mortality rates for specific ages and sexes which are available since 1900 for the Registration Area of that year shows a general decline, both prewar and postwar, for each sex- and age-period, with the postwar decline more rapid than the prewar except for both sexes in the age group of 65 years and over. For the males as a whole, the increased postwar rate of decline was greater than the corresponding trend difference for the females, due to the fact that for the period 15–65 years the trend differences were all considerably greater for males, and thrice and two times as great for the age groups 15–24.9 and 25–44.9. For the age group 45–64.9 the male increase in downward trend is also nearly twice that for the females.

It is evident that the forces responsible for the prewar-postwar alteration in trend have acted on the sexes in a widely different manner throughout the life span. This variation leads to the suspicion that such forces have not been the same at all periods of life, nor for each sex. It is difficult, from a study of the trends, to resist speculation as to what these may be.

For ages under five no sex differences of any consequence are noted. This is to be expected because of similar environmental conditions of life. Environmental improvements, better diagnosis, and especially the purification of milk through pasteurization and the eradication of bovine tuberculosis can reasonably be held to account for prewar-postwar trend differences at these ages.

At ages, 5–14.9, the situation is less clear. One might suppose, because of sex differences in adolescence, that the male trend difference would have been greater than the female. The opposite is actually the case. The conclusion of Gray, mentioned above, may here come into play. It postulates that where tuberculosis rates are highest, they tend to decline fastest. The mean prewar female tuberculosis rate was 39, the corresponding male rate was only 28; the excess in the former may be responsible for the increased female postwar trend over that of the male postwar one. In fact, the female ratio of postwar to prewar trend is 5.3, a value quite similar to the male ratio of 5.6. It is interesting to observe that the female trend-line for this period is rapidly approaching the male one, which points to the possibility that within a few years the female tuberculosis rate for this age period will be less than the male rate. An inspection of chart 4 shows that this period is the only one in which we

may expect, from the past trend-lines, such a reversal of the male-female tuberculosis mortality rates.

After age 15 the behavior of the trend-lines differs widely for one sex as compared with the other. The postwar advantage is all in favor of the males. The postwar male trend-lines for the years between 15 and 65 start in 1921 at a lower level, and decline more sharply than the corresponding female trend-lines. The chief sex environmental difference at these ages is the degree of participation in industry which has altered in a manner consistent with the mortality changes observed here. Before the war the male-trends were the less favorable, and this may be attributed to occupational hazards tending to tuberculosis in the worker, a situation towards the amelioration of which a great deal of attention has been paid in the past fifteen years. On the other hand, women during this time have entered the occupational fields in large numbers, and to this exposure of the sex to new hazards may be attributed in part the failure of the female adult mortality curves to show a postwar change comparable to that of the male.

At the age period over 65, no significant trend difference appears between postwar and prewar periods, but for both sexes the indication is that tuberculosis mortality has been declining less rapidly than before the war. The divergence in actual magnitude of the male and female rates has been growing larger since 1900 or thereabouts, the male rate becoming increasingly larger than the female one. The transfer to these older ages of persons who under former conditions of mortality would have died earlier in life may be a factor here. Aside from this, however, the reasons for these old-age differences are obscure, and at present it can only be pointed out that the decline in tuberculosis mortality is less favorable at these ages than at any other period of the life span.

It is also important to note that at the age-group centering at 20 years of age the man has from every angle a more favorable outlook as far as tuberculosis mortality is concerned than the woman, and aside from the higher female rates for ages 5–14.9, this age-group is practically the only one for which any superiority for males over females is found. Not only does the peak of female tuberculosis mortality occur here, causing female mortality rates to exceed those of the male, but we find that the postwar male rate is declining faster than the female at this one period of life, and that the postwar change in the male trend was over twice as great as the corresponding female trend change.

CONCLUSIONS

1. The downward trend of tuberculosis mortality has been faster since the war than before the war for all states in the Registration Area of 1911 but Vermont.

2. In Vermont the decreased trend may reasonably be attributed to the increasing mortality from tuberculosis among the granite workers of that state.

3. In general the alteration in trend has been greatest in the New England and Atlantic states.

4. The postwar trend has been greater than the prewar trend for both sexes and at all ages except over 65 years in the registration states of 1900.

5. The greatest trend differences were found at the younger age-groups.

6. At ages over 15, the trend differences were greater among males than among females, which may possibly be accounted for on the basis of an improved occupational environment.

7. In 1921, when the characteristic trend for the next decade was initiated, the male trend-lines began at a definitely lower level, compared to the prewar trend level, than did the female trend-lines.

8. Before the war, the female tuberculosis mortality trend was greater than the male thoughout the life span. This was also true of the post-war period, except for the age group, 15–24.9, when the male trend exceeded the female.

BIBLIOGRAPHY

(1) Britten, R. H., and Sydenstricker, E.: Mortality from pulmonary tuberculosis in recent years, Public Health Reports, 1922, xxxvii, 2843.

(2) Krause, A. K.: The decline of tuberculosis mortality in the United States and the influence of the influenza epidemic of 1918, Amer. Rev. Tuberc., 1926, xiii, 385.

(3) Green, H. W.: A graphic analysis of the trends in the tuberculosis death rate, Cleveland Health Council, 1927, 46 pp.

(4) Lee, W. W.: The epidemiology of tuberculosis, past and present, Amer. Rev. Tuberc., 1929, xx, 368.

(5) Putnam, Persis: Sex differences in pulmonary tuberculosis deaths, Amer. Jour. Hyg., 1927, vii, 663.

(6) Sydenstricker, E.: The trend of tuberculosis mortality in rural and urban areas, Amer. Rev. Tuberc., 1929, xix, 461.

(7) DePorte, J. V.: Recorded and resident death rates from tuberculosis in New York State in 1926, Ibid., 1928, xvii, 634.

(8) Dublin, L. I.: The causes for the recent decline in tuberculosis and the outlook for the future. An address delivered before the 19th annual meeting of the N.T.A. at Santa Barbara, Calif., June 20, 1923.

(9) HARMON, G. E.: A study of the problem of obtaining a trend line for epidemiological data, J. Prev. Med., 1929, iii, 139.
(10) FISHER, R. A.: Statistical methods for research workers, ed. 3, London, 1930, 283 pp.
(11) WILLCOX, W. F.: Introduction to the vital statistics of the United States, 1900 to 1930, Government Printing Office, Washington, 1933, 138 pp.
(12) RUSSELL, A. E., BRITTEN, R. H., THOMPSON, L. R., AND BLOOMFIELD, J. J.: Health of workers in dusty trades. II. Exposure to siliceous dust, U. S. Public Health Service Bull., no. 187, 1929, 206 pp.
(13) HOFFMAN, F. L.: The problem of dust phthisis in the granite-stone industry, U. S. Bureau of Labor Statistics, Bull. no. 293, 1922, 178 pp.
(14) GRAY, C. E.: Tuberculosis mortality in the original death registration states, Amer. Rev. Tuberc., 1928, xviii, 687.
(15) U. S. Bureau of the Census. Abstract of the fifteenth Census of the United States, Govt. Printing Office, Washington, D. C., 1933, 968 pp.

TUBERCULOSIS AMONG RURAL AND VILLAGE SCHOOL-CHILDREN IN BUNCOMBE COUNTY, NORTH CAROLINA

P. P. McCAIN, C. D. THOMAS AND H. L. SUMNER

During the past eight years the Extension Department of the North Carolina Sanatorium has been working in coöperation with county health, school and public-welfare authorities in all sections of the State in an effort to make practical application to the school children of the newer knowledge of tuberculosis in childhood and adolescence.

The present study is an example of similar ones which we have made in the same manner in about one-half of the counties in the State on more than 150,000 children, a large proportion of whom were from rural districts. Our available funds have been so limited that we have been unable to assemble detailed statistics on the whole group. The studies have been conducted more on a practical clinical than on a research basis.

Our limited appropriation, however, has been at least in part responsible for what we believe is perhaps one of the most important contributions of the study, which is a demonstration of the extent to which the coöperation of the community official and volunteer agencies can be secured in furnishing the personnel for and in bearing the expense of such studies. This investment of both time and money on the part of the community is, we feel, the surest way of securing lasting results.

THE FIELD OF THE STUDY

This communication comprises a study of the rural and village school-children of Buncombe County in the heart of the Blue Ridge Mountains, of which Asheville (population 50,000), the county-seat, has long been a tuberculosis resort. There are separate city and county health departments, with whole-time physicians as health officers in charge of each. This study was conducted in coöperation with the County Health Department, which has the whole hearted support of the medical profession. The County Health Officer (Sumner) is one of the authors of this report. There is also a separate superintendent for the city and county schools. The children of Asheville are not included, except for those in attendance on three of the suburban schools. The field of the County Health

Department and of the present study includes the whole county outside of Asheville, an area of 682 square miles with a population of 48,000 which is almost entirely rural, the largest town having only 970 inhabitants.

The population is composed almost entirely of white, native-born Americans, most of whom are engaged in farming, dairying, lumbering and fruit-growing, although in three of the communities there are blanket, textile, and furniture manufacturing plants. Only white school-children were included in this study. The few colored children in the whole area attend for the most part small and rather inaccessible schools. There are 41 white schools in the area studied with average enrolment of 326 and a total daily average of 11,542. Most of the children are transported to the schools in busses.

THE PLAN OF CONDUCTING THE STUDY

For several years we studied only those children whose parents gave their written consent. During the past three years and in the present study we "put the shoe on the other foot," so to speak, and investigated all pupils in all the grades except those whose parents sent written requests for exemption, a plan that is much more satisfactory in every way and results in securing 15 to 20 per cent more children for observation.

Various methods (newspaper articles, talks to parent-teachers associations, etc.) are used to advertise the clinic, but the most effective method is by gaining the coöperation of the county superintendent of schools. If enthusiastic and well informed as to the purposes and plans of the clinic, he will instruct his school principals and teachers to lend their hearty assistance. In Buncombe County this attitude was largely responsible for our securing 82 per cent of the average daily attendance for our work.

This was conducted in the same way as the other school-clinics throughout the State, and comprised giving tuberculin tests to the whole group, and in getting histories and general physical and X-ray examinations on the positive reactors. No further observations were made on negative tuberculin reactors. The Extension Department of the State Sanatorium furnished the clinician and X-ray technician, developed and interpreted the films, and classified and made recommendations for each child studied, and also furnished the tuberculin, and all necessary charts and report blanks. The local community under the direction of the County

Health Officer furnished the nurses and necessary clerical service, paid for the transportation of the physician and nurses in the county, provided for the use of a satisfactory high-powered X-ray machine, paid for all X-ray films, transported the children to the X-ray machine, sent out reports to the parents, and did necessary preliminary and follow-up work. Thus a very large proportion of the cost of the clinic was borne by the local community.

The tuberculin tests were all given by one of us (Thomas), the clinic physician, and read by him in forty-eight hours, except in rare instances when they were read in seventy-two hours. The tuberculin used in this work was the product of one of the best commercial biological laboratories, which had been standardized against the international unit. In this clinic, too, as regularly in our school-clinic work, we used only a single dose of 0.1 mgm. (0.1 cc., 1:1000 dilution) of Old Tuberculin intracutaneously, both to save time and because we felt that practically all children with significant infections and lesions respond positively to this dose. Those responding only to larger doses had, we felt, either very mild infections or almost obsolete lesions. We did not intend to determine the total incidence of tuberculous infection in a community, but to locate all children whose infections are clinically and potentially significant. By using this single medium-sized dose, a considerable saving in cost is effected, because of the smaller number of positive reactors needing X-rays, and of the time saved in not repeating the tests on the negative reactors.

It would not be wise to use an initial dose as large as this in clinically sick patients, but we have had no unfavorable results from its use in more than 150,000 children who were well enough to be in school. Very rarely was there local vesiculation and such slight systemic disturbance as mild and temporary fever and malaise was still rarer. Naturally, a larger percentage will give stronger reactions to this dose than to 0.01 mgm.; but the tangible evidence of definite infection, as shown by strongly positive tuberculin reactions is valuable, because it usually causes sufficient alarm in the parent to make him willing to pay for X-ray films for his child, and to have a study made of the whole family in order to locate the source of infection.

The physician and nurse, with the assistance of the teachers, usually test from 400 to 800 children per school day, depending upon number of pupils and distance between schools. After the tests are completed, the nurse and physician return to secure histories and make physical exami-

nations on the positive reactors. Teachers, especially those who have been located in the community for some years, can often supplement the clinical and "contact" information obtained from the children. A general physical examination is made, more to discover other defects than to locate any evidences of tuberculosis in the chest. With a nurse to obtain the history, the physician can usually examine 25 to 40 children per day. Although some think information gained from physical examination does not warrant the time and expense required, we feel that it does, especially since it may point out other defects, if present, and make it much more likely that parents will place their children under their family physicians. This usually results in building up the children, not only by correcting remediable defects, but also by establishing better hygienic and dietary habits and limiting further infection.

After physical examinations, positive reactors are carried, usually in school busses, to have X-ray films of their chests made. In this clinic we use the very satisfactory equipment of the County Health Department in the Court House at Asheville.

The films are all made by the Sanatorium technician, one posteroanterior and one oblique film, on all children not too large for the 11- x 14-inch size. The oblique film not infrequently reveals tuberculous lymph nodes, otherwise obscured by the heart, spine and large blood-vessels. Having exposures in two different planes also assures greater accuracy in the interpretation of questionable densities. On the larger children only one posteroanterior 14- x 17-inch film was taken. With the assistance of nurses and volunteer community workers, the physician and one technician can usually make films on from 20 to 30 children per hour. Only the exposures are made at the clinic, while the films are brought to the Sanatorium to be developed. The latter are "read" by one of us (McCain), and the findings recorded on a diagram, with the history and physical examination in duplicate, one copy for the Sanatorium and the other for the County Health Department.

A report of the results of the study is sent to the parents of each child, with the recommendation that they take the child and the report to the family physician for the correction of any discovered defects and for final advice as to habits and treatment. Some time during the course of the clinic the clinic physician usually talks to the County Medical Society on the purpose of the clinic and the diagnosis and treatment of tuberculosis in childhood. Emphasis is always laid on the importance of discovering the open cases in the home and of preventing further infection.

The cost of the films is about 75 cents per child. A letter is sent to the parents of all positive reactors, requesting that those who can do so pay for their own children's films. In the great majority of the clinics throughout the State we find that parents are usually willing to pay. In our clinic the parents paid $500.00 of these costs, leaving a balance of only $167.00 to be paid by the County. For various reasons it is rarely possible to get X-ray films on all positive reactors. In this clinic 889 out of 1,112 reactors, or 80 per cent, had films made.

STATISTICAL FINDINGS

In the present study, 9,482 pupils, 82 per cent of the average daily attendance, were tested with 0.1 mgm. Old Tuberculin intracutaneously. There were 1,112, or 11.72 per cent, positive reactors. The average for 122,000 children tested by the Extension Department of the North Carolina Sanatorium (1) throughout the State, including 19,000 colored children, was 15.77 per cent positive reactors. Our smaller percentage is doubtless due to the rather large proportion of strictly rural children. In a similar study of school-children in one of the nearby mountain counties, which is altogether rural, there were only 4.3 per cent positive reactors to a similar dose. The percentage of positive reactors in the different schools varied from 3.5 per cent in one of the most isolated schools to 17.6 per cent in a school located in a community in which there were a number of tuberculous families.

The average percentage of reactors, 11.72, is materially lower than that reported by most workers. It is difficult to make accurate comparisons, however, because of the varying conditions under which the studies were made. We also gave this same dose of 0.1 mgm. to 250 teachers in the same schools in which we tested the children. Of these teachers, 41.2 per cent reacted positively, almost four times the percentage of reactors among the pupils.

As is generally the case, the percentage of positive reactors was found to increase with age. In table 1 there is listed by age the number of children tested and the percentage of reactors. The rather high percentage of reactors in the five-year group was due to the fact that a considerable number of these were brought in for study because they were "contacts."

As stated above, we secured X-ray films on 889 of the pupils giving positive reactions. Demonstrable lesions were found by X-ray in 193, or 21.7 per cent, of the positive reactors. There were also 111, or 12.5 per cent, classified as "suspicious." Of the 193 with demonstrable lesions,

173 were classified as having the childhood or primary type, 9 as having the adult or reinfection type, and 11 as having both the childhood and adult types of lesions. Table 1 also shows a classification by age of the X-ray findings. The highest percentages of demonstrable lesions were in the 6-, 8-, 9-, 10- and 12-year-old groups.

TABLE 1

The tuberculin test and the demonstrable lesions by age

AGE IN YEARS	NUMBER TESTED	NUMBER OF REACTORS	PERCENTAGE OF REACTORS	NUMBER HAVING X-RAYS	X-RAYS POSITIVE				X-RAYS SUSPICIOUS	X-RAYS PROBABLY NEGATIVE
					Childhood type	Adult type	Adult and childhood type	Percentage of X-rays positive		
5	45	7	15.5	7	0	0	1	14.3	4	2
6	682	35	5.1	35	8	2	1	31.4	7	17
7	818	46	5.6	31	6	0	0	19.4	6	19
8	916	70	7.6	52	12	0	3	28.8	7	30
9	970	74	7.6	67	22	1	2	32.3	7	35
10	943	112	11.8	91	21	1	2	26.4	14	53
11	922	120	13.0	97	17	0	0	17.5	13	67
12	951	126	13.2	102	28	1	0	28.4	12	61
13	900	105	11.6	92	17	1	0	19.6	9	65
14	703	102	14.5	68	8	0	1	13.2	6	53
15	616	98	15.9	75	12	1	0	17.3	9	53
16	500	103	20.6	80	10	0	0	12.5	7	63
17	262	50	19.0	48	9	1	1	22.9	6	31
18	158	38	24.0	22	2	0	0	9.1	3	17
19	56	17	30.3	13	0	0	0	0	0	13
20	40	9	22.5	9	1	1	0	22.2	1	6
Total.....	9482	1112	11.7	889	173	9	11	21.7	111	585

A comparison of the findings by sex shows a rather remarkable similarity in both the number studied and the percentages of positive reactions and of demonstrable lesions. There were 4,616 girls and 4,866 boys. The percentage of positive tuberculin reactors in the girls was 11.76 and in the boys 11.69. Among 438 girls having X-rays, demonstrable lesions were found in 96, or 21.9 per cent; and of 451 boys, 97, or 21.5 per cent, had demonstrable lesions. The number of adult-type lesions, 13, found in the boys, however, is almost twice the number, 7, found in the girls. Contrary to expectation only two of the adult-type lesions in the girls and only three in the boys were found in the 'teen age-group. For a detailed comparison by sex and by age, the percentages of positive reactors and of the X-ray findings see table 2.

TABLE 2

The tuberculin test and the demonstrable lesions by age

AGE IN YEARS	NUMBER TESTED	NUMBER OF REACTORS	PERCENTAGE OF REACTORS	NUMBER OF X-RAYS	X-RAYS POSITIVE				X-RAYS SUSPICIOUS	X-RAYS PROBABLY NEGATIVE
					Childhood type	Adult type	Adult and childhood type	Percentage of X-rays positive		
Girls										
5	19	4	21.0	4	0	0	0	0	3	1
6	322	18	5.6	18	5	1	0	33.3	2	10
7	416	22	5.2	16	4	0	0	25.0	2	10
8	449	28	6.2	24	5	0	1	25.0	4	14
9	486	42	8.6	32	9	0	0	28.1	3	20
10	443	59	13.3	49	12	1	2	30.6	4	30
11	418	51	12.2	44	7	0	0	15.9	4	33
12	479	68	14.1	51	15	0	0	29.4	6	30
13	450	50	11.1	43	6	0	0	14.0	6	31
14	335	46	13.7	31	3	0	1	12.9	2	25
15	310	49	15.8	40	6	0	0	15.0	4	30
16	268	60	22.3	47	8	0	0	17.0	5	34
17	128	28	21.8	28	7	1	0	28.6	2	18
18	68	14	20.5	8	2	0	0	25.0	0	6
19	12	3	25.0	2	0	0	0	0	0	2
20	13	1	7.7	1	0	0	0	0	0	1
Total.....	4616	543	11.8	438	89	3	4	21.9	47	295
Boys										
5	26	3	11.5	3	0	0	1	33.3	1	1
6	360	17	4.7	17	3	1	1	29.4	5	7
7	402	24	5.9	15	2	0	0	13.3	4	9
8	467	42	8.9	28	7	0	2	32.1	3	16
9	484	32	6.6	35	13	1	2	45.7	4	15
10	500	53	10.6	42	9	0	0	21.4	10	23
11	504	69	13.6	53	10	0	0	18.9	9	34
12	472	58	12.2	51	13	1	0	27.5	6	31
13	450	55	12.2	49	11	1	0	24.9	3	34
14	368	56	15.2	37	5	0	0	13.5	4	28
15	306	49	16.0	35	6	1	0	20.0	5	23
16	232	43	18.5	33	2	0	0	6.1	2	29
17	134	22	16.4	20	2	0	1	15.0	4	13
18	90	24	26.6	14	0	0	0	0	3	11
19	44	14	31.8	11	0	0	0	0	0	11
20	27	8	29.6	8	1	1	0	25.0	1	5
Total....	4866	569	11.7	451	84	6	7	21.5	64	290

The 21.7 per cent of the Buncombe County reactors with X-rays showing demonstrable lesions is almost twice as large as the average percentage which we have found elsewhere. Of 16,097 reactors on whom we have made X-rays in various other parts of the State and on whom we have compiled statistics (1), 11.78 per cent showed demonstrable lesions. This higher percentage in Buncombe County is doubtless due to the fact that a considerably larger proportion of the positive reactors in Buncombe County than in other parts of the State come from "contact" homes. Of the 889 Buncombe County children having X-rays, 335, or 37.7 per cent, gave a history of known contact, and most of these of home contact. As will be seen in table 3 the percentage of demonstrable lesions in this known contact group is 33.7, which is almost three times as high as the

TABLE 3

Classification by history of contact of 889 positive reactors having X-rays

HISTORY OF CONTACT	NUMBER HAVING X-RAYS	X-RAYS POSITIVE					X-RAYS SUSPICIOUS		X-RAYS PROBABLY NEGATIVE	
		Childhood type	Adult type	Childhood and adult type	Total number	Percentage	Number	Percentage	Number	Percentage
Known.....	335	103	5	5	113	33.7	55	16.4	167	49.8
Unknown.....	554	70	4	6	80	14.4	56	10.1	418	75.5
Total.....	889	173	9	11	193	21.7	111	12.5	585	65.8

14.4 per cent of demonstrable lesions in the group in which the source of contact was unknown or not admitted.

The large proportion of the total number of Buncombe County children tested came from strictly rural homes in which opportunities for contact were very slight and the percentage of demonstrable lesions for the total number studied, 9,259 (9,482 less 223 positive reactors which had no X-rays), was only 2.1 per cent; and this is very little higher than the average of 1.6 per cent (1) for the rest of the State.

The intensity of the positive reactions was recorded as one-, two-, three- or four-plus, according to the scale employed by Opie and McPhedran and their associates at the Phipps Institute (2). In table 4 is shown a classification of the 889 reactors studied, and of their demonstrable lesions according to the degree of their reactions. Thirty-three per cent gave one-plus; 27 per cent, two-plus; 39 per cent, three-plus; and 0.5 per cent,

four-plus reactions. Demonstrable lesions were found in only 3.4 per cent of the one-plus, in 20.2 per cent of the two-plus, in 37.9 per cent of the three-plus and in 40 per cent of the four-plus reactors. Densities which were "suspicious" for tuberculosis were found in 8.5 per cent of the one-plus, 11 per cent of the two-plus, 16 per cent of the three-plus and in 60 per cent of the four-plus.

It is noted that, the more severe the tuberculin reaction, the larger the percentage of demonstrable lesions found. This corresponds closely to the results of a similar study of 7,462 white and colored children in Durham County by the Extension Department of the North Carolina Sanatorium, as reported by Easom (3). Although lesions are more likely to be found in those who give the stronger reactions, they occur sufficiently often in the one- and two-plus reactors to make it advisable for them, as well as the stronger reactors, to have films made.

TABLE 4

Classification by degree of reaction of 889 positive reactors having X-rays

	NUMBER OF REACTORS	PERCENTAGE OF REACTORS	DEMONSTRABLE LESIONS				SUSPICIOUS LESIONS	
			Number, childhood type	Number, adult type	Number, adult and childhood type	Percentage of demonstrable lesions	Number	Percentage
1-plus	293	33.0	10	0	0	3.4	25	8.5
2-plus	243	27.3	43	3	3	20.2	27	11.1
3-plus	348	39.2	118	6	8	37.9	56	16.1
4-plus	5	0.6	2	0	0	40.0	3	60.0
Total	889	100.0	173	9	11	21.7	111	12.5

RECOMMENDATIONS FOR TREATMENT

We feel that the first step in the treatment of all children who have positive tuberculin tests, whether they have demonstrable lesions or not, should be the location of their source of contact and the prevention of further infection. To this end we urge that the family physician make tuberculin tests on all members of the family, and that he make a study of all the positive reactors. The latter should consist of a history, physical examination, several examinations of the sputum, if there is any expectoration, and an X-ray if possible. The Extension Department of the Sanatorium furnishes tuberculin to the physicians in the State without charge.

Further treatment for the various groups was recommended as follows: *1:* That those children having positive tests, thus showing the presence of tubercle bacilli, but as yet no demonstrable lesions, be permitted to lead normal lives; but that constitutionally they be built up to the highest possible extent by proper hygienic-dietetic measures, by protecting them against preventable diseases, and by correcting any defects in order that their infections may never develop into disease. *2:* That those with childhood-type lesions of slight or moderate extent and those classified as "suspicious" be allowed to remain at home and continue going to school, provided they can get reasonable hygienic and dietetic care, and that they will avoid strenuous exercise and lie down for an hour either at school or upon returning home in the afternoon, and provided they place themselves under the observation of their physician. *3:* That those with childhood-type lesions of any extent, who have to continue to live in contact with an open case, be placed in a preventorium, unless the contact be otherwise broken or unless the diseased patient is known to take the necessary rigid precautions to prevent further infection of the other members of the family. *4:* That all children with very extensive childhood-type lesions be placed in a sanatorium or preventorium, or that they be placed on a modified rest-cure at home if their home conditions are suitable. *5:* That all children with adult-type lesions, except those that are definitely inactive, and all with plainly caseous tracheobronchial lymph nodes be taken out of school immediately and be kept at bed-rest at home until they can be placed in a sanatorium.

It was recommended for all groups that they have periodic examinations, including X-rays of their chests, at intervals of from a few months to a few years, depending upon the severity of the lesions and upon whether or not there was still exposure to an open case.

On the above basis we advised that 38 of the 193 Buncombe County children having demonstrable lesions be sent to a sanatorium or preventorium, and that the other 155 be allowed to remain at home and most of them permitted to continue their school-work. The tuberculous children of Buncombe County are in an exceptionally favorable position because in and around Asheville, the county-seat, there are a number of unusually well-qualified tuberculosis specialists who are always available for consultation. Since the holding of this clinic there has been a movement on foot for the establishment of a preventorium, which, we understand, bids fair to be successful.

REFERENCES

(1) The North Carolina Sanatorium: Report of children's tuberculosis clinics, Biennial Report, 1931–1932, p. 14.

(2) Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: A survey to determine the prevalence of tuberculous infection in school children, Amer. Rev. Tuberc., 1929, xx, 423.

(3) Easom, H. F.: Childhood tuberculosis In Durham County, North Carolina, Tr. Med. Soc., State of North Carolina, 1932, p. 559.

A FOLLOW-UP STUDY OF THE MEDICAL-STUDENT AND PHYSICIAN PATIENTS DISCHARGED FROM TRUDEAU SANATORIUM, 1916–1931

ROBERT R. BATES[1]

The follow-up records of the 239 medical-student and physician patients discharged from the Trudeau Sanatorium during the fifteen-year period between 1916 and 1931 were examined primarily with a view of correlating the kind and amount of work done during the first and second postdischarge years with the number of relapses that occurred. These 239 cases were taken from, and are part of, the list totalling 3,349 pulmonary-tuberculosis patients discharged from the sanatorium during the same period[2] and comprise 7.1 per cent of the larger group. No suspected or nonpulmonary cases are included. The most recent cases had been followed for one year, the oldest cases for fifteen years; so, presumably, the number of relapses and deaths in the group as a whole was optimistically low. However, in limiting the follow-up in this way, a fairer comparison with the larger group of patients was permitted, since the latter had been reported in this manner.

Twenty-five per cent of the medically educated patients came for treatment while they were still *minimal* cases, as contrasted to 21 per cent in the large lay group. On discharge, 49 per cent of the medical group and only 41 per cent of the large group representing all patients were classified as *quiescent* while the large group showed a corresponding greater proportion of active cases (37 per cent compared to 31 per cent in the doctor-patients). Therefore, the small (medical) group evidently left the sanatorium in somewhat better condition than the others, and also continued to show an advantage as verified by the fact that up to the year 1931, when the time-limit for the study was closed, 10 per cent more of the medical group than of the large group remained well, while 7 per cent more of the latter had died.[3] It should be noted in this connection

[1] Peter Bent Brigham Hospital, Boston, Massachusetts.

[2] Report of Trudeau Foundation, 1931, p. 28.

[3] "Of 143 medical students and doctors admitted to the Trudeau Sanatorium from 1922–1930, 70 per cent were *moderately advanced* or *far advanced*; over the same period of time, 79 per cent of all patients admitted were *moderately advanced* or *far advanced* (classification of 1930 of the National Tuberculosis Association)."—Steidl, John: Tuberculosis among medical students, *American Review of Tuberculosis, 1932, xxvi, no. 1.*

that the condition after discharge of about 4 per cent of the large group of patients unfortunately could not be traced, whereas that of all the medical ones could; but, even if this had been balanced by a 4 per cent failure in follow-ups for the professional patients, they would still have relatively more well and fewer dead at the time the period of observation was closed.

The implication is that the doctor-patients are more careful about what they do than the average ex-patients. But what modifications, if any, in their subsequent work do these medical ex-patients make, and to what degree do these modifications figure in preventing relapses? Some light may be thrown on these questions by learning, for example, how many *moderately advanced* quiescent patients keep well if they undertake a heavy private practice the first and second years after discharge. These first two years are of particular interest because most relapses are known to occur during this period and patients are advised to conduct themselves accordingly. Table 1, therefore, concerns itself with the type and hours of work undertaken for these first two postdischarge years and the status of the patient's health not only during these years, but up to 1931.

The several kinds of work done during both years together, with the extreme and the average daily hours of activity, may be found listed at the top of the table. This work consisted of (a) active, full time internships in general hospitals, averaging 10.6 hours a day and with extremes of from 4 to 14 hours; (b) "full-time" private practice, which is considered to be of equivalent intensity to the interneships (averaging 10.5 hours, with extremes of from 8 to 17 hours); (c) a lighter type of private practice, averaging 6.5 hours, and varying between 3 and 8 hours; (d) attendance at medical schools or postgraduate classes, the conduction of research work, or teaching, averaging as a whole 6.5 hours, and varying between 4 and 14; (e) sanatorium work, done either as a staff doctor or a superintendent, and averaging 7.2 hours and varying between 2 and 16 hours; (f) roentgenology, averaging 8 hours; (g) a miscellaneous group of housekeeping or sales work, amounting to 8 to 10 hours a day; and (h) the resting group, which included in rare cases a few simple duties, such as puttering around a garden or tending chickens.

Approximately 25 per cent of the discharged medical-student and physician ex-patients spent their first postdischarge year resting, while the others did either full-time work (about 20 per cent) or part-time work (the remaining 55 per cent). However, considered from the standpoint of amount of disease, 86 per cent of the *minimal* cases undertook some

TABLE 1

Correlation of kinds of work attempted the first and second years postdischarge with resulting state of health

Type of Work Attempted and Length of Working Day ⟶		1st year post-discharge ⟶	Hospital Interneship, 4–14 hrs. Av. 10.6 hrs.					Heavy Practice, 8–17 hrs. Av. 10.6 hrs.		Light Practice, 3–8 hrs. Av. 6.5 hrs.						Student Research Teaching, 4–12 hrs. Av. 6.5 hrs.						Sanatorium Physician, 2–16 hrs. Av. 7.2 hrs.						Roentgenology, Av. 8 hrs.	Resting, 0–6 hrs. Av. ¼ hr.						Housework, Av. 8 hrs.		Total Cases
		2nd year post-discharge ⟶	Interneship	Heavy Practice	Student-Research	Roentgenology	Resting	Heavy Practice	Resting	Heavy Practice	Light Practice	Student-Research	Roentgenology	Sanatorium M.D.	Resting	Interneship	Heavy Practice	Light Practice	Student-Research	Sanatorium M.D.	Resting	Interneship	Heavy Practice	Light Practice	Sanatorium M.D.	Roentgenology	Resting	Light Practice	Light Practice	Student-Research	Sanatorium M.D.	Saleman, 10 hrs.	Roentgenology	Resting	Light Practice	Housework	
Minimal: 61 cases	Active: 10 cases	Well						1			2								1			1											3				7
		Relapsed																															1				3
		Dead																																			0
	Quiescent: 33 cases	Well	6	2		1		4		2	3								3		1	1			1					1				1		24
		Relapsed							1		2								2			1														7
		Dead																															1				2
	Apparently arrested: 18 cases	Well	1	1	1			4		1	2								2	1					1	1				2							17
		Relapsed										1																									1
		Dead																																			0
Moderately advanced: 151 cases	Active: 51 cases	Well		1				2		3	2					1			4			1			5				1			1	8			29
		Relapsed									1			1	1				1						1				1			1	7			12
		Dead																															8				10
	Quiescent: 75 cases	Well			1			7		2	9					1	1	1	9				2	3	9					2		1	2			50
		Relapsed				2		1		1	3			1	1			1	1		1			1	3					4			4			20
		Dead						1	1		1								1											1			1			5
	Apparently arrested: 25 cases	Well	1					4		2	2		1			2			4						3			1					1				21
		Relapsed																	1						1		1		1							4
		Dead																																			0
Far-advanced: 27 cases	Active: 14 cases	Well												1											1								1	1			3
		Relapsed									1																						1				2
		Dead																												2			6				9
	Quiescent: 11 cases	Well																		2					1						1		1				3
		Relapsed																							1						1						1
		Dead																			1				1		1				1		2				7
	Apparently arrested: 2 cases	Well									1									1																	1
		Relapsed																																			0
		Dead																																			1
Total cases			8	4	2	3	0	24	2	11	29	1	1	2	3	4	1	2	31	2	2	4	2	4	28	1	2	1	3	7	4	1	1	47	1	1	239

degree of work the first postdischarge year, as compared to 74 per cent of the *moderately advanced* and 44 per cent of the *far-advanced* cases. And it would be expected that, the less the disease, the sooner one could plan on going to work.

Table 1 shows much more clearly the degree of success these patients had in keeping their health while working than could be explained in the text; so to prevent tedious reading this table is depended upon to provide the detailed information for any specific kind of work done in each of the two years by all the different types of patients. As an example of the use of this table, one, wishing to know if a *minimal quiescent* case may with fair safety plan to go back to one or more years of active interneship, sees

TABLE 2

Proportion of patients remaining well with the various kinds of work undertaken during the first year after discharge

MINIMAL		TYPE OF WORK ATTEMPTED	MODERATELY ADVANCED		AVERAGE HOURS OF WORK PER DAY	FAR ADVANCED	
Number of patients	Per cent well		Number of patients	Per cent well		Number of patients	Per cent well
12	91	Hospital	5	60	10.6		
10	80	Heavy private practice	16	81	10.5		
13	80	Light private practice	31	68	6.5	3	30
10	70	Student-Research teacher	29	79	6.5	3	0
6	83	Sanatorium M. D.	30	73	7.2	5	40
		Sanatorium Supt. Roentgenologist	1	100	8.0		
1	100	Housework			8.0	1	100
9	66	Resting	39	44	0.5	15	20
61	78	Total	151	64		27	26

that over the fifteen-year period nine tried it and only one relapsed, six of the nine safely continued their interneships the second year, and the remaining two went into heavy private practice the second year and kept their health. Another example from the table: one *far-advanced*, apparently arrested case thought he was well enough to go back to a student's life the first year and work in a sanatorium the second, and he died.

Looking at the list of ex-patients starting in hospital work, regardless of the amount of disease or the degree of activity on discharge, it is seen that about 82 per cent stayed well. In the arduous private-practice group, 81 per cent continued well, as did 68 per cent of those in light

private practice. Seventy-one per cent of the student group, 71 per cent of the sanatorium-workers' group, and only 41 per cent of the resting group continued well, as would be expected if the sicker patients were the ones confined to light work or to continued rest. Table 2, illustrating these results, when split up into *minimal* or *moderately advanced* or *far-advanced* cases, summarizes the high spots of the study, since it shows the proportions in each group remaining well.

Thus in review:

1. The admission and discharge condition of the medical group was compared to the large group, and it was noted particularly that only a slightly greater proportion of medically educated patients came early for treatment, but they left on the whole, in better condition than did the general run of patients.

2. The kinds of work undertaken during each of the two years after discharge may be seen in table 1, together with the average hours and extreme hours, and the number of persons remaining well, the number relapsing and staying alive, and the number dead; the work being shown separately for each classification of patient according to the current American Tuberculosis Association Standards. An epitome (table 2) lists the percentages remaining well at each kind of work.

3. The majority of patients who "get by" their first year seem also to get by their second one, that is, 82.8 per cent were well at the end of the first and 63.9 per cent were still well at the end of the second year; and more of these had increased their work the second year than had decreased it.

4. Those undertaking arduous work on discharge (interneships and heavy private practice) are largely confined to the *minimal* (quiescent and arrested) and the *moderately advanced* groups.

5. It seems that what one does on leaving the sanatorium is not the only important factor concerned in attempting to stay as well as on discharge. The need for continuing with rest or partial rest is of relatively poorer prognostic import, whereas the ability to begin with a full day of work points to the likelihood of permanent health. Most of the cases that relapsed came from the "resting" and limited-work groups (39 per cent "broke again") and not from the "hard-working groups" of which only 19 per cent failed to remain well.

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THE INCIDENCE OF TUBERCULOUS INFECTION AND DISEASE IN A PRIVATE SCHOOL FOR BOYS[1]

THOMAS N. HORAN[2]

The present study extends over a period of three years and includes roentgen examinations and tuberculin tests on 197 cases (average age between 14 and 15 years); in most cases both the roentgen examinations and tuberculin tests have been repeated at yearly intervals. The roentgenograms were interpreted by Doctors William A. Evans, Henry D. Chadwick, Lawrence Reynolds, E. R. Witwer, and Richard Morgan.

There were 21 students, or 11 per cent, showing a definite childhood type of tuberculosis (about the average incidence in the United States). The diagnosis in this series depended upon the presence of nodules in various phases of calcification in the parenchyma, or in lymph nodes at the lung root. There were no adult forms of tuberculosis in the school (Chadwick reports one case in every 460 Detroit high school children (1)).

It is important to understand the meaning of this lesion encountered in 11 per cent of adolescent children. The relation between open cases of adult tuberculosis and the development of the childhood type is well established. In the present series 80 per cent of boys with positive roentgenograms offered a definite history of tuberculosis in the immediate family. Elsewhere, studies on children known to be exposed have shown an increased incidence of childhood tuberculosis in the roentgenogram.

Apart from these epidemiological facts, and the valuable clue they offer in the removal of contacts, the importance of the discovery by roentgenogram of childhood tuberculosis is less meaningful. With the exception of cases occasionally seen in infants, the clinical manifestations are meagre. The diagnosis itself is based usually upon roentgen evidence of deposits of calcium which have taken about two years to form. Table 1 shows, as have similar statistical summaries, an absence of relationship between the presence of tuberculosis and such various factors as age, weight, height, generalized lymph-node enlargement, red blood count, haemoglobin, Dick test, history of measles, whooping cough, pneumonia,

[1] The Cranbrook School, Bloomfield Hills, Michigan.

[2] Detroit, Michigan.

other serious diseases, and allergy. In the present series, as in all such studies, there were no characteristic physical findings.

The intracutaneous tuberculin test was given in dilutions of 1:10,000 and 1:100 and in a few special cases of 1:10. Each boy in the school was tested early in the spring of 1932 and of 1933, and in the fall of 1933. The percentage of boys with a positive Mantoux reaction was 41. This may be compared with studies reported in corresponding age groups in London, England, 48 per cent (2); Minnesota, 31 per cent (Pirquet test) (3); New York City, 67 per cent (4); California, 46.6 per cent (5); Detroit, 25 per cent (Pirquet test) (6). The relation between the Mantoux readings and the roentgen diagnosis was of special interest. *All*

TABLE 1

	CHILDHOOD TYPE OF TUBERCULOSIS	NORMAL
Age	15.1	15.4
Weight	128	132
Height	66.3	66.7
Lymph-node enlargement	5%	8%
Red blood cells	4,550,000	4,600,000
Haemoglobin	80%	82%
Dick +	37%	42%
Measles	87%	83%
Whooping-cough	88%	73%
Pneumonia	0%	12%
Other serious diseases	19%	26%
Allergy	43%	38%

roentgenograms were interpreted without previous knowledge of the Mantoux test. Sixty-two per cent of the boys with a roentgen diagnosis of the childhood type of tuberculosis showed a positive Mantoux test; 38 per cent, however, were negative to tuberculin in dilutions of 1:10,000 and 1:100 and in 4 instances of 1:10. This is a surprising finding (although similar reports are encountered in the literature). Explanations are interesting. Dow and Lloyd, in the *British Medical Journal*, are inclined to believe that such densities shown in the X-ray cannot be tuberculous but must be interpreted otherwise. Careful autopsy studies, however, as the work of Opie, have "shown these lymph nodes—partially or completely calcified—are always an indication of tuberculous infection" (7). A second explanation, entirely in accord with the results of

the present study, supposes that the positive tuberculin readings approach and reach a negative, as healing in the lesion progresses.

Before reporting the changes in tuberculin sensitiveness, it is necessary to explain that the environment at the school is known, as far as possible,

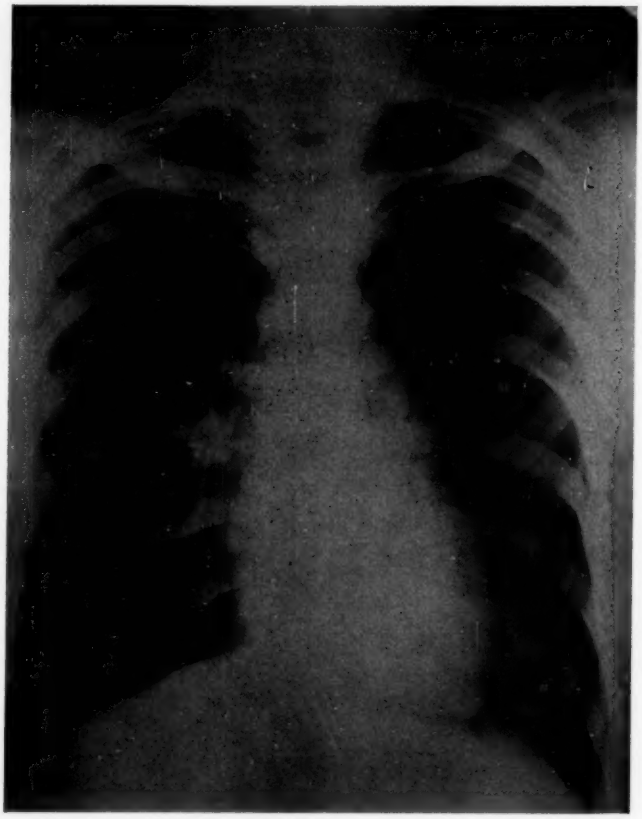

FIG. 1. Case of childhood tuberculosis, showing the turning point from a positive to a negative intracutaneous test

	1:10,000	*1:100*	*1:10*
1932	−	+	
1933	−	−	±
1934	−	−	−

to be free from open cases of tuberculosis. The chest of each boy has been roentgenographed; faculty, maids, workmen and their families have been examined and roentgenograms frequently taken; the girls at Kingswood School, an adjoining girls' boarding-school, which shares in the

social life at Cranbrook, have been carefully examined by Dr. Campbell Harvey. A group of boys in a boarding-school is a relatively segregated and cloistered section of society.

The percentage of positive Mantoux reactions in the three successive school years was 47, 41 and 33 per cent,—a definite progression toward a negative test. This may be presented in another way; 116 of the Mantoux tests changed in degree of reaction from one year to the next; 85 (77 per cent) were observed to pass from a positive toward a negative Mantoux reaction, while in 31 (23 per cent) the reaction increased in a positive direction. Of the tests which did not change from year to year, 85 per cent had already turned negative, and it is probable that by increasing the amount of tuberculin the depths of the negative readings could be plumbed, and a recession into a deeper negative uncovered from year to year. (See figure 1.) This shift toward a negative Mantoux test has occurred in a group growing older in years, and in whom an increase in the percentage of positive Mantoux reactions could be expected.

Two representative reports which may seem in disagreement with the belief that positive Mantoux readings, in the absence of contacts, tend to become negative are briefly considered:

1: Lloyd and Macpherson (8) in the *British Medical Journal* state that a tuberculin test once it becomes positive "persists throughout childhood in 96 per cent of cases." The children in this series, however, were members of the general population in London, England, inevitably in contact with tuberculosis, and cannot be compared with the group at a boarding school.

2: Wolff, Stone and Eberson (9) in a study of 100 children, age 3½ years, summarized: "no calcifications, fibrotic spot, lymph node tumor, or localized pulmonary infiltration shadow is found in the tuberculin negative group." The present study finds changes typical of childhood tuberculosis, with a negative tuberculin test in 38 per cent of its total number of cases. It is probable that the tuberculin test had at one time been positive in this series and that, with healing of the lesion, after an interval of several years had become negative.

SUMMARY

In a group of 197 students, 41 per cent give a positive Mantoux test and 11 per cent show the characteristic roentgen findings of the childhood type of tuberculosis.

A relation between the tuberculin tests and the state of activity of the

childhood type of tuberculosis is described. After about two years calcium is deposited in an appreciable degree in the tuberculous lymph nodes, and healing progresses, in the absence of further contacts, with a fading of the tuberculin test from year to year until in some cases a negative tuberculin test may be reached.

REFERENCES

(1) CHADWICK, H. D.: Tuberculosis in children and adolescents, J. Mich. M. Soc., 1932, xxxi, 109.

(2) DOW, D. J., AND LLOYD, W. E.: Comparative study of chest radiograms and Mantoux tests in children, Brit. M. J., April 16, 1932, i, 701.

(3) STEWART, C. A.: Pulmonary disease, 5,816 cases in children; with special reference to the childhood type of tuberculosis, Amer. J. Dis. Child., 1932, xliii, 803.

(4) BARNARD, M. W., AMBERSON, J. B., JR., AND LOEW, M. F.: In adolescents; a study of 1,000 children (school) in New York City made under the auspices of Bellevue-Yorkville Health Demonstration in 1930, Amer. Rev. Tuberc., 1931, xxiii, 593.

(5) DICKEY, L. B., AND SEITZ, R. P.: Incidence of infection in children based on 3,500 intracutaneous tests, Ibid., 1933, xxiii, 13.

(6) METZGER, H. C.: Childhood tuberculosis, J. Mich. M. Soc., 1933, xxxii, 349.

(7) NORRIS AND LANDIS: Saunders, ed. 4, 1929.

(8) LLOYD, W. E., AND MACPHERSON, A. M. C.: Reinvestigations of children previously examined, Brit. M. J., May 13, 1933, i, 818.

(9) WOLFF, E., STONE, R. S., AND EBERSON, F.: Juvenile tuberculosis suspects; evaluation of clinical and roentgenological findings in relation to diagnosis and grade of tuberculin reaction, Amer. Rev. Tuberc., 1932, xxv, 738.

TUBERCULOSIS AMONG UNIVERSITY OF WISCONSIN STUDENTS[1]

R. H. STIEHM

Relatively recent observations of roentgenograms showing minimal tuberculous infiltration of the lungs definitely lead one to the conclusion that early diagnosis of the disease—when treatment is most effective—must be dependent upon methods other than physical examination. Such minimal infiltrations, usually occurring in the apical and subclavicular regions, and usually not accompanied either by symptoms or physical signs, frequently progress to become active positive-sputum cases. Through the medium of the roentgenogram, however, minimal infiltration can be detected long before physical signs and symptoms make their appearance.

During the past year, a program has been instituted in the Department of Student Health, not only to discover clinically active cases of tuberculosis, but to make possible detection in its earlier stages, when symptoms and physical signs of the disease are not yet manifest. The program has, likewise, served in teaching tuberculosis and case-finding methods to senior medical students.

All students enrolled in the University for the first time were given, as part of their routine physical examination, intracutaneous tuberculin tests. Those showing positive reactions were further studied by means of a complete medical history, physical examination, and a single postero-anterior roentgenogram of the chest. When indicated, stereograms, oblique and lateral views were taken. It is interesting to note that in the fourteen-year period from 1919 to 1933, an average of 10 cases of pulmonary tuberculosis per year was discovered. During the present school year a total of 43 cases was found. This is an increase of 430 per cent over the fourteen-year average. Of these 43 cases, 17, as compared with a yearly average of 4, were advised to withdraw from school,—an increase of 425 per cent. Of the number withdrawing, 12 are known to have entered sanatoria for care, an increase of 480 per cent as compared to the previous average of 2.5 per cent per school year. Of the 17 cases with-

[1] From the Department of Student Health, University of Wisconsin, Madison, Wisconsin.

drawing from school, 11 were found in students other than those entering the University for the first time. The greater use of the tuberculin test and roentgenogram, plus a staff more attentive to tuberculosis, are the probable factors accounting for the larger number of cases found.

TUBERCULIN TESTS

The intracutaneous test was used. Students were given 0.1 mgm. of Old Tuberculin Saranac Laboratory. Those showing no reaction were, in most instances, given a subsequent test with 1.0 mgm. As will be noted in the accompanying tables, the groups from 17 to 20 years, containing the largest number of students, show approximately 6.0 per cent more reacting to 1.0 than to 0.1 mgm. In no instance were constitutional symptoms of reportable degree noted as a result of the test, and the number of sore arms from four-plus reactions was too negligible to indicate the use of tuberculin in a smaller amount.

TABLE 1

Pulmonary tuberculosis among students, June, 1919, to June, 1934

SCHOOL YEAR	NUMBER OF CASES	NUMBER WITHDRAWING FROM SCHOOL WITH ACTIVE TUBERCULOSIS	NUMBER ENTERING SANATORIA
1919–1920	8	3	1
1920–1921	15	5	2
1921–1922	15	4	2
1922–1923	19	9	6
1923–1924	14	5	4
1924–1925	9	1	0
1925–1926	7	4	2
1926–1927	7	1	1
1927–1928	10	8	8
1928–1929	5	2	2
1929–1930	5	4	1
1930–1931	11	9	4
1931–1932	3	0	0
1932–1933	10	4	2
1933–1934	43	17	12

In table 2 the percentage of reactions according to age is given. In the yearly age-groups from 17 to 25, which contain the largest number of students, a steady increase with age is apparent. The age-groups from 11 to 16 inclusive are from the University High School. Of 124 pupils, 26, or 21 per cent, showed positive reactions.

Table 3 lists the number of reactors in the age-period from 17 to 20 inclusive, in which the largest number of students fall. At 17, 22.6 per cent of the girls and 25.9 per cent of the boys showed reactions. At the age of 20, both groups showed reactions of approximately 32.3 per cent.

Each year the College of Agriculture offers to students, coming largely from rural Wisconsin, a short course in agriculture. Of 70 students tested, only 4, or 5.7 per cent, reacted (table 4).

The incidence of infection among medical students was found to be larger than in the general student body. Of 93 first-year medical students, 45.1 per cent showed positive reactions. In the fourth-year class of 40 students, 22, or 55.0 per cent, showed reactions. Of a group of 25 nurses entering training, 28.0 per cent reacted. The results are indicated in tables 5, 6, and 7.

Table 8 gives a short summary of all tuberculin tests done during the school year.

GROUPING ACCORDING TO RESIDENCE

All Wisconsin students tested were grouped according to their county and post-office address. Those from outside the State were grouped according to their respective States, or native country.

In Wisconsin, where numbers from counties are large enough to warrant consideration, it is interesting to note that Milwaukee county, with a first-year student enrollment of 254, leads with a percentage of positive reactors of 36.6 per cent. Dane county, in which Madison is located, with a first-year enrollment of 374, has a percentage of 28.6 per cent, which very closely approaches that of the entire group tested.

The respective number of students from middle-Western and Eastern States is too small to risk much in the way of generalization. However, of 165 students tested from 6 States of the North Central Division (Illinois, Indiana, Iowa, Michigan, Minnesota and Ohio) 44, or 28.7 per cent, reacted positively. Of the 110 students coming from Eastern States, (New England, New York, New Jersey, and Pennsylvania) 53, or 48.2 per cent, showed positive reactions.

Students from foreign countries, three from China, three from Sweden, and one each from England, Germany, Mexico, and Switzerland, gave the highest incidence of infection; 7 of the 9, or 77.7 per cent, having positive tests. However, no conclusions may be drawn from such small numbers.

TABLE 2

Tuberculin reactions according to age, 1933–1934

AGE	NUMBER TESTED	POSITIVE TO 0.1 MGM.		POSITIVE ONE +		POSITIVE TWO +		POSITIVE THREE +		POSITIVE FOUR +		POSITIVE TO 1 MGM. BUT NEGATIVE TO 0.1 MGM.		POSITIVE ONE +		POSITIVE TWO +		POSITIVE THREE +		TOTAL POSITIVE TO 0.1 MGM. AND 1 MGM.	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
11	13	2	15.4					2	15.4											2	15.4
12	15	2	13.3			1	6.6	1	6.6											2	13.3
13	15	3	20.0	1	6.6	2	13.4					1	6.7	1	6.7					4	26.7
14	18	1	5.6	1	5.6							3	16.7	1	16.7					4	22.2
15	20	2	10.0	1	5.0			1	5.0			1	5.0	1	5.0					3	15.0
16	43	8	18.6	4	9.3	1	2.3	3	7.0			3	7.0	3	7.0					11	25.6
17	348	60	17.2	29	8.4	24	6.9	7	2.0			22	6.3	22	6.3					82	23.6
18	621	122	19.6	61	9.8	53	8.5	8	1.3			34	5.5	27	4.3	7	1.1			156	25.1
19	430	94	21.8	48	11.6	42	9.8	4	0.9			23	5.3	19	4.4	2	0.5	2	0.5	117	27.2
20	262	68	26.0	31	11.8	33	12.2	4	1.5			18	6.9	14	5.3	4	1.5			86	32.8
21	155	40	25.8	14	9.0	16	10.3	10	6.5			8	5.2	3	1.9	5	3.2			48	31.0
22	121	36	29.7	11	9.1	16	13.2	8	6.6	1	0.8	5	4.1	5	4.1					41	33.9
23	61	22	36.1	7	11.5	10	16.4	5	8.2			3	4.9	2	3.3	1	1.6			25	41.0
24	64	24	37.5	4	6.3	13	20.3	7	10.9			5	7.8	3	4.7	2	3.1			29	45.3
25	60	18	30.0	1	1.7	15	25.0	1	1.7	1	1.7	3	5.0	2	3.3	1	1.7			21	35.0
26	22	11	50.0	3	13.7	5	22.7	3	13.7											11	50.0
27	16	9	56.3	5	31.3	4	25.0					2	12.5	2	12.5					11	68.8
28	17	7	41.2	3	17.6	3	17.6	1	5.9			1	5.9	1	5.9					8	47.1
29	8	3	37.5	1	12.5			2	25.0			1	12.5	1	12.5					4	50.0
30	8	4	50.0	2	25.0			2	25.0											4	50.0
31	4	4	100.0	1	25.0	3	75.0													4	100.0
32	10	4	40.0	1	10.0	1	10.0	2	20.0											4	40.0

33	9	7	77.8	1	11.1	6	66.7					1	11.1	1	11.1					8	88.9
35	5	3	60.0	1	20.0			1	20.0	1	20.0									3	60.0
36	5	3	60.0			2	40.0	1	20.0											3	60.0
37	2	2	100.0			1	50.0	1	50.0											2	100.0
38	2	2	100.0			2	100.0													2	100.0
39	2	2	100.0			2	100.0													2	100.0
40	3	3	100.0			3	100.0													3	100.0
44	1	1	100.0			1	100.0													1	100.0
52	1	1	100.0	1	100.0															1	100.0
Total.....	2,351	568	24.1	232	9.9	259	11.0	74	3.2	3	0.1	134	5.7	110	4.6	22	0.9	2	0.09	701	29.8

TABLE 3

Intracutaneous tuberculin test, September, 1933*

AGE	NUMBER TESTED	POSITIVE TO 0.1 MGM.		POSITIVE ONE +		POSITIVE TWO +		POSITIVE THREE +		POSITIVE TO 1 MGM. BUT NEGATIVE TO 0.1 MGM.		POSITIV ONE +		POSITIVE TWO +		POSITIVE THREE +		TOTAL POSITIVE TO 0.1 MGM. AND 1 MGM.	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Men																			
17	131	24	18.3	16	12.2	7	5.3	1	0.8	10	7.6	10	7.6					34	25.9
18	351	64	18.2	36	10.3	25	7.0	3	0.9	20	5.7	17	4.8	3	0.9			84	23.9
19	271	57	21.0	33	12.1	22	8.2	2	0.7	18	6.6	15	5.5	2	0.7	1	0.4	75	27.6
20	154	39	25.3	21	13.6	16	10.4	2	1.3	11	7.1	9	5.8	2	1.3			50	32.4
Women																			
17	208	35	16.8	13	6.2	16	7.7	6	2.9	12	5.8	12	5.8					47	22.6
18	232	49	21.1	19	8.2	25	10.8	5	2.1	14	6.0	10	4.3	4	1.7			63	27.1
19	117	27	23.0	12	10.2	13	11.1	2	1.7	4	3.2	3	2.4			1	0.8	31	26.2
20	68	17	25.0	3	4.4	13	19.1	1	1.5	7	7.3	5	5.2	2	2.1			24	32.3

* Saranac Laboratory Old Tuberculin.

TABLE 4

Intracutaneous tuberculin test, short course in agriculture, November, 1933: students from rural Wisconsin*

AGE	NUMBER TESTED	POSITIVE TO 0.1 MGM.	NEGATIVE TO 0.1 MGM.	PER CENT POSITIVE TO 0.1 MGM.
17	2	0	2	0
18	15	0	15	0
19	22	0	22	0
20	11	2	9	9.1
21	8	1	7	12.5
22	4	0	4	0
23	3	1	2	33.3
24	0	0	0	0
25	3	0	3	0
26	2	0	2	0
Total.....	70	4	66	5.71

* Saranac Laboratory Old Tuberculin.

ROENTGENOGRAMS

In the interpretation of roentgenograms, numbering in excess of 500, it is quite probable that no two examiners working separately on the same group of films would arrive at the same interpretations. As concerns

TABLE 5

Tuberculin tests, Freshmen Medical Students, 1933–1934

AGE	NUMBER TESTED	POSITIVE TO 0.1 MGM.		POSITIVE ONE +		POSITIVE TWO +		POSITIVE THREE +		POSITIVE FOUR +		POSITIVE TO 1 MGM. BUT NEGATIVE TO 0.1 MGM.		POSITIVE ONE +		POSITIVE TWO +		TOTAL POSITIVE TO 0.1 MGM. AND 1 MGM.	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
19	1	0	0.0									0	0.0					0	0.0
20	6	0	0.0									0	0.0					0	0.0
21	27	9	33.3	1	3.7	5	18.5	3	11.1			4	14.8	2	7.4	2	7.4	13	48.1
22	20	7	35.0			3	15.0	3	15.0	1	5.0	2	10.0	2	10.0			9	45.0
23	11	5	45.4	1	9.0	3	27.2	1	9.0									5	45.4
24	11	5	45.4			3	27.2	2	18.1									5	45.4
25	8	3	37.5			3	37.5											3	37.5
26	1	1	100.0					1	100.0									1	100.0
27	3	2	66.6	1	33.3			1	33.3									2	66.6
28	2	1	50.0	1	50.0													1	50.0
32	1	1	100.0			1	100.0											1	100.0
35	1	1	100.0					1	100.0									1	100.0
37	1	1	100.0					1	100.0									1	100.0
Total..	93	36	38.7	4	4.3	18	19.4	13	14.0	1	1.1	6	6.5	4	4.3	2	2.2	42	45.1

TABLE 6

Tuberculin tests, Senior Medical Students, 1933–1934

AGE	NUMBER TESTED	POSITIVE TO 0.1 MGM.		POSITIVE ONE +		POSITIVE TWO +		POSITIVE THREE +		POSITIVE TO 1 MGM. BUT NEGATIVE TO 0.1 MGM.		POSITIVE ONE +		TOTAL POSITIVE TO 0.1 MGM. AND 1 MGM.	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
23	5	4	80.0	3	60.0			1	20.0					4	80.0
24	12	4	33.3			3	25.0	1	8.3	1	8.3	1	8.3	5	41.7
25	3	2	66.7			2	66.7			1	33.3	1	33.3	3	100.0
26	6	3	50.0	1	16.7	1	16.7	1	16.6					3	50.0
27	2	0	0.0							1	50.0	1	50.0	1	50.0
28	2	1	50.0	1	50.0									1	50.0
29	2	1	50.0					1	50.0					1	50.0
30	2	0	0.0											0	0.0
32	3	1	33.3					1	33.3					1	33.3
33	1	0	0.0							1	100.0	1	100.0	1	100.0
35	1	1	100.0	1	100.0									1	100.0
40	1	1	100.0			1	100.0							1	100.0
Total.....	40	18	45.0	6	15.0	7	17.5	5	12.5	4	10.0	4	10.0	22	55.0

calcified hilum nodes in first-infection tuberculosis, it is frequently difficult to decide whether calcification has occurred. That more first-infection type of tuberculosis existed in the group studied is probable, for in most instances only single posteroanterior views of the chest were obtained. With only the single view, 24.2 per cent, approximately one of four roentgenograms taken on tuberculin-positive reactors, showed evidence of first infection.

Comparison of results would probably show greater agreement in interpreting infiltration of the adult type of tuberculosis. When suspicion existed relative to a shadow in the single film, stereograms were requested. The lesions were classified (table 10) as infiltration with symptoms or

TABLE 7

Tuberculin tests, nurses, 1933–1934

AGE	NUMBER TESTED	POSITIVE TO 0.1 MGM.		POSITIVE ONE +		POSITIVE TWO +		POSITIVE THREE +		POSITIVE TO 1 MGM. BUT NEGATIVE TO 0.1 MGM.		POSITIVE ONE +		TOTAL POSITIVE TO 0.1 MGM. AND 1 MGM.	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
18	2	0	0.0							0	0.0			0	0.0
19	6	1	16.7			1	16.7			1	16.7	1	16.7	2	33.3
20	5	1	20.0			1	20.0							1	20.0
21	7	2	28.6	1	14.3			1	14.3					2	28.6
22	1	0	0.0							0	0.0			0	0.0
23	3	1	33.3	1	33.3									1	33.3
25	1	1	100.0			1	100.0							1	100.0
Total...	25	6	24.0	2	8.0	3	12.0	1	4.0	1	4.0	1	4.0	7	28.0

physical signs and infiltration without symptoms or physical signs. Of the total of 26 infiltrations found, 5 were thought to require treatment necessitating withdrawal from school. Of these 5, one had symptoms and physical signs, while four had neither. Two students studied are of sufficient interest to warrant mention.

One, a boy of nineteen, had his first roentgenogram in January, 1934. He had no symptoms or physical signs, was active in sports, and had gained 10 lbs. since entering school in the fall. His X-ray showed a rather soft bilateral apical and small subclavicular infiltration, well out in the periphery on the right. The films and a letter suggesting that he withdraw from classes were sent to his family physician, who was not convinced that treatment was

necessary, and the boy returned to school. Comparing a film taken in March with the one taken in January, no change was noted. In May the student was requested to report for progress study. He had no symptoms, had gained 8 more pounds, and would not admit that he felt anything but fit. Physical examination of the chest was essentially negative. He had no fever. A

TABLE 8

Tuberculin tests according to groups, 1933–1934

GROUPS	NUMBER TESTED	NUMBER POSITIVE	PERCENTAGE	NUMBER NEGATIVE	PERCENTAGE
High-school students:					
Boys	37	7	18.9	30	81.1
Girls	43	10	23.3	33	76.7
Total	80	17	21.3	63	78.7
Students entering September, 1933:					
Men	1,163	346	29.8	817	70.2
Women	753	226	30.0	527	70.0
Total	1,916	572	29.9	1,344	70.1
Students entering February, 1934:					
Men	109	35	32.1	74	67.9
Women	79	23	29.1	56	70.9
Total	188	58	30.9	130	69.1
Short Agriculture Course	70	4	5.7	66	94.3
Total	70	4	5.7	66	94.3
Nurses, February, 1934	25	7	28.0	18	72.0
Total	25	7	28.0	18	72.0
Medical students:					
First-year class	93	42	44.7	51	55.3
Fourth-year class	40	22	55.0	18	45.0
Total	133	64	47.4	69	52.6
Grand total	2,412	722	29.9	1,690	70.1

blood-sedimentation test, white blood count and differential, and roentgenogram were requested. The blood sedimentation report was returned from the laboratory before the roentgenogram. On two former occasions, it had been normal, but now showed an 18-mm. fall in one hour. It heralded the spread noted on the X-ray, for the infiltration in the left subclavicular area

had spread to the level of the 3rd anterior rib and the 7th posterior spine. At present, he is at home under the family physician's care, who states that he is fever- and symptom-free, and that he has noted no abnormal physical signs in his chest. His roentgenogram of July, 1934, showed some clearing on the left, but there is now present a 4-mm. cavity in the left subclavicular region. Tubercle bacilli have not been found in his sputum.

Another student entering the University for the first time in February, 1934, gave a history of a loss of 5 lbs. in the fall of 1933, with some fatigue noted at

TABLE 9

Roentgenological examination

	NUMBER	PER CENT	PERCENTAGE* OF TOTAL NUMBER OF STUDENTS RECEIVING TUBERCULIN TEST
Number given examination..... 529			
Number with no evidence of pulmonary tuberculous lesion....	374	70.7	91.2
Number with first-infection type of tuberculosis visible on single posteroanterior roentgenogram.....	128	24.2	7.3
A-Primary nodule (Ghon tubercle)..... 21			
B-Primary nodule with calcified hilum lymph nodes. 7			
C-Calcified hilum lymph nodes..... 100			
Number with reinfection or adult-type of tuberculous infiltration.....	26	4.9	1.5
Number with miliary tuberculosis (healed by calcification).....	1	0.2	0.06
Total.....	529	100.0	100.06
Number with lesions necessitating withdrawal from school for treatment.....	5	0.9	0.2

* These figures are arrived at by assuming that all negative reactors would show no tuberculous lesion on X-ray.

that time. A roentgenogram showed right subclavicular and apical infiltration, rather soft in character. The patient refused to consider treatment other than increased rest-hours and some reduction in his usual athletic activities. Progress films of his chest showed continuous clearing of the shadow, its softness becoming strand-like in character. The blood-sedimentation test and differential blood counts were, at all times, normal. At no time was a fever observed.

These two cases, having similar shadows when first observed, but progressing very differently, seem to indicate that the only course to

follow, until more is learned of these early lesions, is one of close surveillance of all infiltrations discovered.

It will be noted in table 9 that, of the positive reactors receiving roentgenograms, approximately 5 per cent showed evidence of an adult type of infiltration, but of this number only 1 per cent had lesions neces-

TABLE 10

Classification of reinfection or adult-type of infiltration

	NUMBER	INFILTRATION OF TOTAL RECEIVING ROENTGENOGRAMS	INFILTRATION OF TOTAL RECEIVING TUBERCULIN TEST
		per cent	*per cent*
Infiltration with physical signs or symptoms referable to the lesion	7	1.3	0.4
Infiltration with neither physical signs nor symptoms referable to the lesion	19	3.6	1.1

Infiltration with physical signs or symptoms referable to the lesion

A-*Minimal* (4)	B-*Moderately Advanced* (2)	C-*Far Advanced* (1)
Apical infiltration	Right subclavicular infiltration with two 8-mm. cavities..... 1	Bilateral lesions above 3rd rib and 7th vertebral spine..... 1
Right..... 1	Lower two-thirds of left lung..... 1	
Left apical and subclavicular..... 1		
Bilateral..... 2		

Infiltration with neither physical signs or symptoms referable to the lesion

A-*Minimal* (18)

1-Apical infiltration
- Right..... 1
- Left..... 6
- Bilateral..... 4

2-Subclavicular infiltration
- Right..... 2*
- Left..... 1

3-Other areas of infiltration
- Second right anterior intercostal space..... 2
- Second and third right anterior intercostal space..... 1
- Right apical extending below clavicle. 1

B-*Moderately advanced* (1)

Bilateral apical and right subclavicular infiltration to 3rd rib and 6th vertebral spine 1

* Infiltration with calcified right hilum lymph nodes.

sitating withdrawal from school. Assuming that all negative reactors would show no lesions if X-rayed, the number of the entire group studied showing adult-type infiltration would be 1.5 per cent, with 0.2 per cent having lesions necessitating withdrawal from school.

Table 10 shows that of the 26 infiltrations of the reinfection type, 19, or 73 per cent, were unaccompanied by symptoms or physical signs.

Evidence of calcification was found in only one of the 26. Further observation is indicated to note the frequency of calcification of primary infection in those later developing the reinfection type of tuberculosis. If, as indicated in these 26 cases, calcification is less frequent in those developing the adult type of tuberculosis, it may turn out that healing with calcification is, in some way, protective.

Of 40 fourth-year medical students, roentgenological study showed calcified hilum nodes in 3, or 7.5 per cent, and a minimal right apical infiltration in 1, or 2.5 per cent.

The first-year medical class of 93 showed 6, or 6.2 per cent, having calcified hilum nodes, and 2, or 2.1 per cent, apical infiltration. None of the lesions found gave evidence of being active.

A study of 25 nurses on admission to training showed calcified hilum nodes in 2, or 8 per cent, and in no case evidence of adult-type infiltration.

SUMMARY

1. The institution of a definite case-finding program among students has made possible a large increase in the number of cases of pulmonary tuberculosis found,—430 per cent above a fourteen-year average.

2. During the school year 1933–1934, 2,412 students were tuberculin-tested, of which number 30 per cent showed positive reactions.

3. In the various tuberculin-tested groups, the smallest per cent of positive reactors occurred among 70 students from rural Wisconsin (5.71 per cent). Of 165 students from six North Central States (Illinois, Indiana, Iowa, Michigan, Minnesota and Ohio) 28.7 per cent were positive. Of the 110 students from Eastern States (New England, New Jersey, New York, and Pennsylvania) 48.2 per cent showed positive reactions.

4. Roentgenological examination indicated that approximately 5 per cent of the positive reactors, or 1.5 per cent of all tuberculin-tested students, had adult-type tuberculous infiltration. Approximately 1 per cent of the positive reactors and 0.2 per cent of those tuberculin-tested had lesions requiring sanatorium treatment.

5. Small round flocculent infiltrations, though not extensive and not accompanied with symptoms or physical signs, appear to be unstable. Either they heal, leaving a strand-like shadow, or progress with the production of symptoms and physical signs. The blood-sedimentation rate, in a case mentioned, was the one additional aid in determining early tuberculous activity, before symptoms and physical signs were manifest.

A STUDY OF THE RACIAL INCIDENCE OF TUBERCULOSIS IN THE PROVINCE OF MANITOBA[1,2,3]

CHARLES H. A. WALTON

This study was undertaken in June, 1933,[4] to learn the racial incidence of tuberculosis in Manitoba as shown by records of deaths. As the enquiry developed other data were secured which are also discussed in this paper. After consideration it was decided that an intensive study of the year 1932 should be made because it was found that it was the first year in which complete data were available.

It has long been known that people of Indian blood suffer a high tuberculosis death-rate and this has become more and more evident as mortality statistics of Indians have been more accurately recorded. But, as will be shown, data even of treaty Indians have been difficult to get accurately, and no separate statistical information has ever been collected about people of part Indian blood (half-breeds). Most of these half-breeds have been classed as European, in origin, in vital statistics, on account of the white part of their ancestry and a few have been placed in the Indian classification.

It was considered that the most satisfactory method of study would be to examine each original certificate of death filed in the Vital Statistics Department of the Provincial Department of Health and Public Welfare. In this study names of people, who from place of residence, or other reason, might be thought to be of partial Indian extraction, were noted. The family history of each of these was investigated by means of the Public Health Nursing Service or otherwise, and it was thus possible to ascertain with a fair degree of accuracy the ancestry of the suspected individuals. The half-breed deaths recorded in the study can thus be said to be accurate in that they are all well-investigated cases. Obviously there may be some further half-breeds missed by this method, but the total can, at least, be said to be minimal.

[1] Presented at a meeting of the Winnipeg Medical Society in April, 1934.

[2] From the Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba.

[3] Awarded Prowse Prize for Clinical Research by the Faculty of Medicine, the University of Manitoba, May, 1934.

[4] Carried out under the Fenton Bequest, 1933–1934.

An arbitrary classification of "Indian" and "half-breed" became necessary. It has long been known that many Indians who live on reserve and "take Treaty" have various admixtures of white blood; indeed on many reserves that is true of all the inhabitants. It is commonly stated that scarcely any pure-blooded Indians remain in Manitoba except possibly in the hinterland. Practically all Manitoba Indians, then, are of mixed blood. In addition there are many people of mixed blood who are not on reserves and who are not classified or known as Indians and who are, of course, citizens of the province. Some of these, in appearance and ways of life, are scarcely distinguishable from ordinary citizens while others are scarcely distinguishable, in all characteristics, from Indians on reserve. Accordingly we have classified as "Indian" all those who "take Treaty," and live on reserve, and the occasional known Indian who for some reason has recently left the reserve. As half-breeds, we have classified all those who are known to have a definite and obvious admixture of Indian blood which may vary from as little as an eighth to as much as seven-eighths. Half-breeds, of course, are not on Treaty and are usually not classed as such (or as Indians) in official statistics.

As half-breeds have never been enumerated as such in the census, at least since 1885, we have had considerable difficulty in arriving at an approximate estimate of the half-breed population. Records of a census in 1885, which we have, show that the small province of that day contained 5,575 Indians and 7,985 half-breeds (*cf.* 15,479 Indians in 1932). By means of a wide inquiry and some actual enumeration we have arrived at what must be a conservative estimate of 20,000 half-breeds in Manitoba in the proportions of 12,000 French, 4,000 Scotch, and 3,000 English with an indeterminate group of 1,000.

Obviously the taking of a number of half-breeds from the various European lists has necessitated a re-study of these groups. Table 1 shows the number of tuberculosis deaths in each racial group and the death-rate per hundred thousand for each group.

Certain important conclusions can be drawn from the above table. As expected the Indian rate is high. For the first time it is definitely demonstrated that the half-breed rate is high; it is only about one-third of the Indian rate but over nine times the "white" rate. It is of particular interest to note the effect of removing the load of half-breed deaths from the French, English and Scotch deaths. For example, the French death-rate without removing the French Indian factor would be in the neighborhood of 100 instead of 25.7, and the Scotch rate would

TABLE 1

Tuberculosis deaths in 1932 classified according to racial origin

RACIAL GROUP		NUMBER OF DEATHS	POPULATION	RATE PER 100,000
Indians				
Died on reserve	106			
Died elsewhere	21	127	15,479	820
Half-breeds				
Usually classed as French	33			
Usually classed as English	5			
Usually classed as Scotch	20	58	(20,000)	(290) (estimated)
Total with Indian blood		185	(35,479)	(521) (estimated)
Other races				
British				
English and Welsh (less half-breed)		44	169,992	25.9
Scotch (less half-breed)		27	108,326	25.0
Irish (less half-breed)		24	77,559	34.9
Others (Dominions, colonies, etc.)		0	5,133	
Total British		95	361,010	27.1
French (less half-breed)		9	35,039	25.7
Slavic				
Polish		32		
Ukrainian		25		
Austrian		14		
Hungarian		1		
Russian		5		
Cheko-Slovak		1		
Galician		1		
Roumanian		3		
Ruthenian		4		
Serbian		1		
Total Slavic		87	140,718	61.9
Scandinavian				
Icelandic		7		
Swedish		5		
Danish		2		
Total Scandinavian		14	31,397	44.6
Germanic				
German		7	23,094	30.3
Mennonite		6	14,984	40.0
Total Germanic		13	38,078	34.2
Latvian		1		

TABLE 1—*Concluded*

RACIAL GROUP	NUMBER OF DEATHS	POPULATION	RATE PER 100,000
Finnish	1		
Hebrew	1		
Chinese	3		
Negro	1		
Total Miscellaneous	7		
Total non-Indian	225	673,961	33.4
Total all tuberculosis deaths (1932)	410	709,000	57.9

be doubled. The peoples originating in Central Europe which we have loosely grouped under "Slavic" show a rate about twice as high as the others. Two other smaller groups show rates above average, namely the Scandinavian and the Mennonite. In Canada the Scandinavian peoples have always been known to have a high morbidity rate. The Mennonites, although of German origin, form a distinct group from the public health point of view.

The fall of the tuberculosis death-rate in Manitoba from something over 150 per 100,000 population, a quarter of a century ago, appears favorable. But, when it is considered that the former rate of 150 took in not one Indian death and probably few half-breeds, while the rate of 1932 carries a very heavy load of both, the actual true reduction is much greater than represented by a drop from 150 to 57.9. In fact, if a curve is plotted of the yearly death-rates a fairly steady fall will be noticed until about 1926, when the curve flattens out and falls much more slowly. This is due to the fact that Indian deaths were not incorporated into Manitoba Vital Statistics by the Dominion Government until 1926 and not by the Manitoba authorities until 1929. Since the province took over this work the Indian statistics have been recorded with increasing accuracy and in increasing volume until in 1932 we find that 31 per cent of the total recorded tuberculosis deaths in Manitoba were of treaty Indians. Thus the rate of 57.9 without the Indian element becomes 41.5 and, as has been stated, records of those in outlying districts, which would include most of the half-breeds, have only recently been accurately re-

corded, so that these people occupy a much more prominent part in the records than a quarter of a century ago. It will be seen from table 1 that, if all people with Indian blood are removed, the "white" rate falls to 33.4 per 100,000 and from the above considerations this would be a more comparable figure with that of about 150 twenty-five years ago.

ACCURACY OF INDIAN STATISTICS

It was recently suggested that the tuberculosis death-rate in Manitoba was noticeably higher than in the other prairie provinces and that that was due to the probable greater incidence of half-breed and Indian tuberculosis deaths in this province. Wodehouse (1) quoted figures tending to show that this was not the explanation but he used only official figures in regard to Indians and half-breeds and I will show that these are entirely inadequate.

As pointed out above, the official (Dominion) figures for Indian vital statistics have always included a small number of half-breeds if the latter term was used on the certificate of registration. Thus, when the group "Indian and half-breed" in *Dominion Bureau of Statistics Reports* is reported, it means all the Indians registered plus a few half-breeds and that most of the half-breeds are included in the European groups.

Table 2 shows the Indian deaths, by years, from all causes and from tuberculosis as published by the Dominion Bureau of Statistics, and as published by the Provincial Vital Statistics Department. The apparent increase in total and tuberculosis deaths each year is due practically entirely to the fact that until very recently little was done to collect complete Indian Vital Statistics. I am informed that 1932 was the first year that the records were fairly complete. The increase is therefore more apparent than real. Further it should be pointed out that the larger Dominion totals are due to the fact that the Dominion has, so far, classified as Indian all who are referred to as half-breeds in the death registrations. If its Indian group took in all people of Indian blood it would be of some value, but since it only adds a few non-treaty half-breeds to the Indian total and calls the resultant figure Indian while the larger mass of half-breeds remain classified as French, Scotch or English, according to how they appear on their death registrations, nothing is accomplished but confusion. The provincial figures are accurate for treaty Indians but the province is unable to give complete half-breed statistics because of lack of information as to their racial origin. To sum up: the Dominion figures, including some half-breeds, are too high for

true Indian statistics and too low for statistics on all with Indian blood (that is, including half-breeds). For practical purposes the provincial figures are accurate, but tend to be low as Indians who die off the reservation may be classified otherwise.

TABLE 2

Deaths of Manitoba Indians, by years, as recorded by the Dominion of Canada and the Province of Manitoba

YEAR	DOMINION		PROVINCE OF MANITOBA	
	Deaths from all causes	Deaths from tuberculosis	Deaths from all causes	Deaths from tuberculosis
1926	137	39		
1927	190	51		
1928	205	72	Prov. took over 1929	
1929	340	73	255	63
1930	260	86	203	66
1931	304	107	248	84
1932		147†	265	119*

* This figure (119) is official provincial total and differs from my 127 because I found 6 additional Indian tuberculosis deaths in 1932 during my search of the records and subsequent investigation.

† This figure (147) is the official Dominion figure and is noticeably larger than mine or that of the province because of its partial load of half-breeds as described above.

Table 3 is taken from the official Dominion records, and although it has all the inaccuracies referred to above it is interesting for comparative purposes. Note the relatively low Indian death-rates for tuberculosis in the Eastern Provinces and in Saskatchewan.

TABLE 3

Populations and tuberculosis deaths by provinces from Dominion of Canada (1931) records at Ottawa, showing Indians separately

	POPULATION	INDIAN POPULATION	PER CENT	TOTAL TUBERCULOSIS DEATHS	RATE	INDIAN TUBERCULOSIS DEATHS	RATE
All Canada	10,362,833	117,322	1.1	7,616	*73*	672	*573*
Prince Edward Island	88,038	233	0.3	68	77	1	429
Nova Scotia	512,846	2,191	0.4	524	102	12	548
New Brunswick	408,219	1,685	0.4	339	83	8	475
Province of Quebec	2,874,255	12,312	0.4	3,178	111	24	195
Ontario	3,431,683	30,368	0.9	1,728	50	113	372
Saskatchewan	921,785	15,268	1.7	326	35	79	517
Alberta	731,605	15,249	2.1	382	52	157	1,030
British Columbia	694,263	24,599	3.5	642	92	171	695
Manitoba	700,139	15,417	2.2	429	61	107	694
*Manitoba**	709,000	15,479	2.17	410	58	127	820

* Manitoba statistics for 1932 from this study.

Note the high Tb. death rates in Nova Scotia and New Brunswick in spite of their small proportion of Indians (0.4 per cent). Note also that the Indian rate in Quebec approaches the rather high total rate. Note the high rate in British Columbia. It is said that its high rate is due, in part, to the fact that invalids go to that province if they can afford to, thus swelling its mortality records.

EFFECT OF IMMIGRATION

Table 4 shows in a tabular manner the apparent fact that the tuberculosis death-rate is higher among immigrants than among people born in Canada or the U. S. A. Note that 65 per cent of the "white" population was born in Canada but suffered only 48.5 per cent of the tuberculosis deaths. This factor of immigration is most noticeable among the Germanic peoples, particularily the Mennonites, in whom only 10 per cent of the population is immigrant, but in the immigrant group 69 per cent of the tuberculosis deaths occurred.

TABLE 4

Non-Indian tuberculosis deaths classified as to place of birth

RACIAL GROUP	NUMBER OF DEATHS		POPULATION	
	Born in Canada	Born outside of Canada	Born in Canada	Born outside of Canada
		per cent		*per cent*
British	60	35 (36.7)	267,081	106,992 (28.6)
Slavic	30	57 (65.5)	50,320	90,395 (64.2)
Scandinavian	8	6 (42.8)	19,766	11,931 (37.6)
Germanic	4	9 (69.2)	34,517	3,561 (9.4)
Others	9	7 (43.7)	65,248	23,710 (26.6)
Totals	111	114 (51.5)	436,932	236,582 (35.1)

EFFECT OF URBAN RESIDENCE

Wodehouse (1), in his recent review, suggested that the higher death-rate in Manitoba may be due, in part, to the effect of the large metropolitan area of Winnipeg. Without going into a detailed analysis, it is sufficient to say that there were only 100 tuberculosis deaths from Greater Winnipeg (corrected for residence), which, with a population of 281,000 gives a death-rate of 35.5 per 100,000, which is well below the crude rate for the province as a whole. In general, the rural and urban rates are much the same. Those rural districts and unorganized territories, containing large half-breed populations and having primitive living conditions, have much higher rates.

EFFECT OF HOSPITALIZATION

In view of the importance of the fact that deaths from an infectious disease such as tuberculosis should occur in hospitals it is interesting to find that 69 per cent (157 out of 225) of the non-Indian tuberculosis deaths occurred in hospitals; while 33 per cent (19 out of 58) of the half-breed deaths and only 10 per cent (13 out of 127) of the Indian deaths occurred in hospitals. A study of the records also shows, as is always found, that there is a very high tuberculosis death-rate among mental hospital patients (24 deaths in about 2,400 patients in 1932).

AGE AT DEATH

The numbers dying in each age-group are shown in table 5, by races. It will be seen that the bulk of the deaths occur in the first three decades of life and the totals rapidly fall off in the later decades. However, when

one considers the population of each age-group it is found that the rate does not fall off, but even tends to rise in the later decades. The lowest rates are found in the first two decades and if the Indian deaths are removed the rates in the first two decades are found to be much reduced comparatively. This is shown in chart 1 graphically.

TABLE 5

AGE-GROUP	NON-INDIAN	HALF-BREED	INDIAN	TOTAL
Under 1 year	5	1	6	12
1 year to 4 inclusive	6	8	7	21
5 to 9	3	6	14	23
10 to 14	10	5	17	32
15 to 19	14	5	17	36
20 to 29	50	14	24	88
30 to 39	41	9	14	64
40 to 49	40	6	6	52
50 to 59	24	1	11	36
60 to 69	25	2	4	31
70 to 79	6	1	6	13
80 and over	1	0	1	2
Total	225	58	127	410

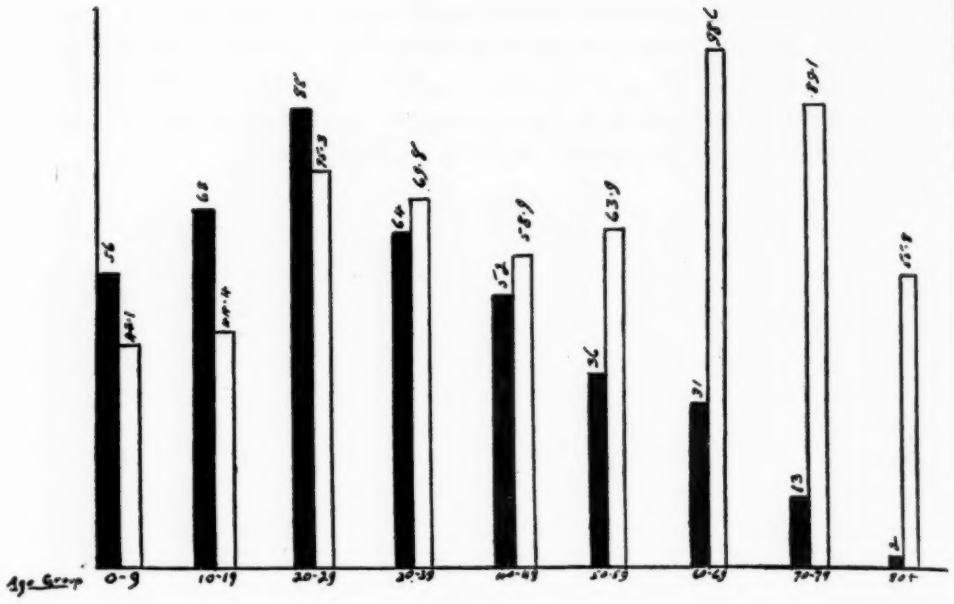

CHART 1

Explanatory Notes

The black areas represent the actual number of deaths in each decade (for 1932) of life. The light areas represent the death-rates per hundred thousand population in each age-group as computed from the 1931 census. The totals are for all races in the province.

Note the steady fall in number of deaths from the third decade on. However, the population of each decade falls in an almost parallel manner so that the death-rates in each adult group are much the same. It would thus appear from these few figures that tuberculosis is a disease which affects all adults to a more or less equal extent.

If the Indian totals are subtracted from those shown above it will be seen that the rates are relatively low in the first two decades but make little difference in the other decades. The rates of the first two decades become 21.6 and 22.0, respectively.

PROBLEMS IN DIAGNOSIS AND CLASSIFICATION

These problems resolve themselves into two; first, the training and qualifications of the diagnostician and his opportunities for making a correct diagnosis; and second, the proper coding and classifications of deaths.

An examination of the death certificates for 1932 showed that 78 of the total 410 tuberculosis deaths were signed by laymen, missionaries, registrars, officials and others without medical training. These all occurred in the remote and unsettled sections of the province and were chiefly among Indians and half-breeds. That tuberculosis is rife among these

people is unquestioned and a large proportion of tuberculosis deaths is expected, but under such conditions there is no certainty. Even with every modern assistance, diagnosis is not always certain. One suspects that where tuberculosis is prevalent there is a tendency to allow the poor Indian to die of nothing else than tuberculosis. For example, one certificate of death of an Indian states that the man was known to have advanced mitral stenosis but died of tuberculosis. It is easy to understand a layman confusing the bloody sputum of mitral stenosis with the haemoptysis of tuberculosis. In connection with the possibility of overdiagnosis it is worth remarking that the Indian tuberculosis death-rate in Saskatchewan is about half that in Manitoba and that the Indians are all much more accessible in that province than in Manitoba.

The second group of problems has to do with the proper coding and classification of deaths. In this connection vital statisticians do the best they can with the resources and guides they have, but when the records are examined from the medical viewpoint some curious results are found. When the certifier is a physician and clearly states that the individual died of a definite form of tuberculosis classification is easy. But when the physician states he saw the patient postmortem and made a diagnosis on hearsay some doubt naturally arises. Two such records were noted. Further, when the physician qualifies his diagnosis in an ambiguous manner, confusion results unless the department is able to get more definite information. Space does not permit recording fully the reports of some 15 cases in which considerable doubt arose, but some indication of their types may be given. One man died of carcinoma of the oesophagus and tuberculosis was given as the secondary cause of death. Investigation showed that his tuberculosis was healed. Under the rules of vital-statistics reporting tuberculosis takes precedence over carcinoma, although this was certainly not a tuberculosis death. Another case was that of a man who died suddenly from a strangulated inguinal hernia, and an unsuspected active pulmonary tuberculosis was found at autopsy. Many other examples could be given of similar cases presenting much difficulty in classification. During this study three clear-cut nontuberculosis cases were removed from the original tuberculosis totals by the department, but several others were left that could not be changed without more definite information or a change in the guiding rules used internationally in vital statistics. We believe that the possible error from this source would not exceed two per cent. The possible error from lay diagnosis is probably much more important.

SUMMARY AND CONCLUSIONS

1. In an endeavor to ascertain the racial incidence of tuberculosis in Manitoba a minute study was made of all deaths classified as from tuberculosis in 1932. This necessitated the examination of all the original certificates of death in that year. The racial strains of those who died were determined and compared with the population as given in the 1931 decentennial census. Where the census was defective—chiefly in relation to half-breeds—the census data were corrected and supplemented.

2. It was shown that, of 410 tuberculosis deaths, 127 were of treaty Indians. Diagnosis in this group was found to be especially open to question.

3. Records of Indian deaths were found to have been very incomplete until the collection of Indian vital statistics was undertaken by the province in 1929, and since then to have become increasingly accurate. Until 1932 many Indian deaths were not recorded. There has been no aggreement as to the definition of *Indian* with resulting inconsistencies and discrepancies. In this enquiry the taking of "treaty" was held to define the Indian.

4. It is also shown that at least 58 tuberculosis deaths occurred among people of sufficiently obvious Indian admixture to be termed half-breed. Formerly a few of these would have found their way into the Indian group, but the majority were classified as European in the French, Scotch or English groups.

5. The number of half-breeds in Manitoba is not known. An estimate is made of 20,000 in the probable proportions of 12,000 French, 4,000 Scotch, and 3,000 English.

6. The tuberculosis death-rate among people without Indian blood was shown to be 33.4 per 100,000 population. This would show considerable progress in the attack on tuberculosis in Manitoba, as this figure is comparable with a rate of about 150 a quarter-century ago.

7. The death-rate for Greater Winnipeg, corrected for residence, was found to be 35.5 and therefore of the same order as that of the white races of the province as a whole.

8. The French death-rate and, to a lesser extent, the English and Scotch is seen to be considerably lowered by counting the people known as half-breeds separately.

9. The official tuberculosis death-rate for Manitoba in 1932 is 57.9

per 100,000 population. The study now reported shows elements that tend to keep this rate high.

10. Certain white racial strains show a tuberculosis mortality above the average, notably the Slavic group with a rate of 62 and the Scandinavian with a rate of 44.

11. Fifty-one and a half per cent of the non-Indian deaths occurred among immigrants who numbered only 35 per cent of the population.

12. In 1932, over 69 per cent of the non-Indian deaths occurred in hospitals or sanatoria; 33 per cent of half-breeds and only 10 per cent of Indians died in such institutions.

13. A study of the ages at death showed that in the white population the death-rate was relatively low in the first two decades of life and higher in the third and succeeding decades.

14. The question of accuracy of diagnosis is discussed and it is noted that 47 per cent of Indian deaths and 30 per cent of half-breed deaths are notified by nonphysicians.

In conclusion, I must express my appreciation of the help given me by Dr. D. A. Stewart, Superintendent of the Manitoba Sanatorium Board; Mr. A. P. Paget, Recorder of Vital Statistics in Manitoba; Mr. A. G. Lawrence, Secretary, Department of Health, Winnipeg; the Dominion of Canada Bureau of Statistics; and Miss Wilson, R. N., and the other members of the Public Health Nursing Service of Manitoba.

REFERENCES

(1) WODEHOUSE, R. E.: Tuberculosis in Canada. (Read before the Canadian Public Health Association at St. John in June, 1933.)
(2) International list of the causes of death.
(3) Manual of joint causes of death, 1925; ed. 2, Bureau of Census, Washington, U. S. A.
(4) Seventh census of Canada, 1931, Bulletins nos. 1, 15, 22. 27 & 29.

THE AGE DISTRIBUTION AND PATHOGENESIS OF TUBERCULOUS MENINGITIS IN CHILDREN[1]

MORRIS SIEGEL

AGE DISTRIBUTION

The fact that tuberculous meningitis occurs frequently in children has been known as long as the disease itself. As early as 1768, Robert Whytt mentioned this fact in the first accurate clinical account of the condition in his *Observations on the Dropsy in the Brain*. His study was based on "about twenty patients," all children, of whom "only one was under half a year old, the rest between two and sixteen." Furthermore, tuberculous meningitis was also recognized as "by far the most frequent of the acute inflammatory disorders of the brain in children, especially from the age of two years to that of puberty" (Gerhard, 1834).

However, there was disagreement as to the age-group most frequently involved. About 70 per cent, or 23 out of Gerhard's 32 postmortem cases of tuberculous meningitis occurred in children between four and seven years old. In 1843, Rilliet and Barthez, from their tabulation of 33 cases to which they added 132 cases of Guersant and Piet, concluded that the condition occurs most frequently between six and ten years, and least frequently between one and two years of age. In 1888, Bosselut reported 117 cases in infants younger than one year, collected from clinical records in hospitals from 1876 to 1887. Ten of these 117 infants were two months old or younger, two were only twenty-one days old and one was only fifteen days old.

The data for determining the details of the age distribution were not yet wholly reliable, for the correctness of the diagnosis was still questionable. One had to wait until 1882 for Koch to demonstrate the tubercle bacillus in order to make the pathological diagnosis unquestionable. In addition, the clinical diagnosis could be verified only after Quincke in 1891 introduced the lumbar puncture, and Lichtheim in 1893 found the tubercle bacilli in the spinal fluid. After this time a mass of reliable

[1] From the Pediatrics Service of Doctor Bela Schick, Mount Sinai and Sea View Hospitals, New York City.

pathological and clinical data slowly accumulated; and there appeared in the past thirty years the statistics of such workers as Holt and Neal in America, and of Koch and Engel in Europe. These authors agreed that tuberculous meningitis occurs most frequently in the first three years of life.

Our knowledge of the age frequency of tuberculous meningitis is incomplete. Some of the details of its occurrence in the first, second and third years are not well known. What happens before six months of age has not been analyzed. For the group ranging from birth to three months, either tuberculous meningitis has been considered as rare or has not been mentioned at all. Furthermore, the frequency of tuberculous meningitis in children who died from tuberculosis has not usually been discussed.

In order to aid in clarifying these issues, the results of a study of 742 cases of lethal tuberculosis are presented. This material, in part, was obtained from 140 consecutive necropsies by Prof. Carl Sternberg, on children who died from tuberculosis at Josef-Kinderspital, in Vienna, from 1923 to 1931. The remaining cases were collected in New York City from the clinical records of 344 children who died of tuberculosis at Mount Sinai Hospital from 1913 to 1934; and from the records of 258 children who died of tuberculosis at Sea View Hospital from 1924 to 1934. In addition, clinical and postmortem records of tuberculous meningitis and lethal tuberculosis reported in the literature in the past thirty years are included, as are also the published accounts of either congenital or acquired tuberculosis in infants dying before the age of six months.

Tuberculous meningitis was found in 445 of the 742 cases of lethal tuberculosis from Josef-Kinderspital, Mount Sinai and Sea View Hospitals. The distribution by years of the 445 cases of meningitis is shown in table 1. This table also includes, for comparison, the results of other workers who noted the distribution of cases of tuberculous meningitis in each year of childhood. Of the 1,522 cases of tuberculous meningitis tabulated in table 1, the greatest number occurred in the second year. Next in order of frequency was the first year and then the third. In these first three years, there was a total of 873 cases (57 per cent). In the next three years the frequency was still high, with 394 cases (26 per cent). After the sixth year there were 255 cases (17 per cent).

If to the 873 cases in the first three years (table 1), one adds 415 reported by Neal, Jackson and Appelbaum, 60 by Kinnear, and 224 by Fothergill and Sweet, there is a total of 1,572 cases of tuberculous menin-

gitis in the first three years. The age distribution of these 1,572 cases is 497 (31 per cent) in the first year, 644 (41 per cent) in the second year, and 431 (28 per cent) in the third year. Therefore, the differences in the number of cases in the first, second and third years seem to become more marked as the total number of cases during this age-period increases.

The age distribution of tuberculous meningitis in each quarter of the first and second years was studied in 397 cases (table 2). In the first quarter year of life, there were only 4 cases. This rarity of tuberculous

TABLE 1

The distribution by year of cases of tuberculous meningitis in childhood (below 13 years)

SOURCE	TOTAL	AGE IN YEARS														UNKNOWN
		0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	12–13	13–16	
Josef-Kinderspital	100	26	21	16	10	8	9	1	2	1	2	2	1	1		
Mount Sinai	302	55	64	54	39	20	18	14	15	8	5	2	5	3		
Sea View	43	5	14	8	2	1	2	1	3	1	0	0	1	1	5	
Total	445	86	99	78	51	29	29	16	19	10	7	4	7	5	5	
Engel	172	46	30	23	12	15	11	7	1	11	6	4	6			
Fabris	59	19	14	7	4	6	3	2	1	1	1	0	1			
Koch, H	351	55	70	59	53	27	18	24	14	8	10	3	6	4		
Lafarcinade	42	5	13	11	4	1	3	1	1	0	0	0	0	1		2
Meyers	105	8	25	32	15	12	6	2	2	1	0	1	1			
Paterson	70	15	15	13	7	6	6	2	1	3	2					
Plischke	100	13	13	16	13	13	6	4	7	4	3	2	2	2		2
Rich and McCordock	72	15	18	13	10	4	1	3	3	0	2	1	1	1		
Wangenheim	106	14	30	18	12	9	8	5	4	1	3	2				
Total	1522	276	327	270	181	122	91	66	53	39	34	17	24	13	5	4
Per cent of total		18.1	21.4	17.7	11.9	8.0	5.9	17.0								

meningitis in the first three months keeps down the total for the first year. The greatest number of cases occurred between the ages of nine and fifteen months. The twelve-month period in which tuberculous meningitis occurred most frequently was between six and eighteen months. During this period there occurred about 27 per cent of all the cases of tuberculous meningitis in childhood. The frequency in each half of this period is about the same.

The four cases listed in the first quarter year of life (table 2) occurred in the third month. There were no cases of tuberculous meningitis in

the first and second months. This fact stimulated a search for the youngest undoubted case of tuberculous meningitis reported in the literature. The data of 3,124 cases of tuberculous meningitis, reported by various investigators[2] who stated the age of the youngest child in their series, were studied. In no instance was the age below two months. In several instances, the youngest age was given as two months (Fothergill, Sweet; Plischke; Orosz). In an additional 485 cases (Engel; Holt; McClelland; Wangenheim), the lowest age limit was not definitely given but was reported as below three months or six months of age.

TABLE 2

The distribution of cases of tuberculous meningitis in each quarter of the first and second years

SOURCE	AGE IN MONTHS								TOTAL FOR FIRST TWO YEARS	TOTAL CASES REPORTED*
	0–3	3–6	6–9	9–12	12–15	15–18	18–21	21–24		
Josef-Kinderspital	0	15	7	4	11	3	5	2	47	100
Mount Sinai	0	11	14	30	24	13	14	13	119	302
Sea View	0	1	1	3	6	3	3	2	19	43
Total	0	27	22	37	41	19	22	17	185	445
Holt	3	23	28	44	24	22	8	9	161	218
Lafarcinade	1	2	1	1	4	5	2	2	18	42
Meyers	0	1	5	2	5	8	8	4	33	105
Total	4	53	56	84	74	54	40	32	397	810
Per cent of total	0.5	6.5	6.9	10.0	9.0	6.6	4.9	3.9	49.0	

* Refers to the total cases of tuberculous meningitis in childhood with the exception of Holt's series in which the children are three years or younger.

The cases of tuberculous meningitis reported by Bosselut, which occurred under two months of age, have already been mentioned. These cannot be accepted, for they were taken from clinical diagnoses recorded at a time before the lumbar puncture was in use. In 1925, Herben and Asserson, in their study of 435 death certificate records of tuberculous meningitis in New York City, noted the case of an infant one month and twenty-five days old. Obviously, a death-certificate record, with its absence of clinical findings, of results of lumbar puncture and of necropsy,

[2] Fothergill, Sweet; Ghon, Kudlich, Winternitz; Geipel; Hartwich; Kinnear; H. Koch; Koplik; Kment; Meyers; Neal, Jackson, Appelbaum; Orosz; Paterson; Plischke; Rich, McCordock; Rosenblum, Makler; Steinmeyer.

is too inadequate to make this case acceptable. Finally, one should note that, in a table of 82 postmortem cases reported by Rich and McCordock in 1933, the age of case no. 11,151, in which tuberculous meningitis was found, was given erroneously as six weeks instead of six months.[3]

In addition, the causes in 68 cases of all types of acute meningitis in infants under two months of age were studied from the reports of various investigators (Barron; Fothergill, Sweet; Holt, Koplik; Neal). The causative agents that were isolated in these 68 cases were as follows:

	cases		cases
Streptococcus	24	*Influenza bacillus*	2
Colon bacillus	20	*Micrococcus catarrhalis*	2
Pneumococcus	11	*Bacillus lactis aerogenes*	1
Meningococcus	7	*Bacillus pyocyaneus*	1

In these 68 cases, there was not one case of tuberculous meningitis.

Another and perhaps better way to understand the occurrence of tuberculous meningitis in the first few months of life is to study its relationship to lethal tuberculosis during this early period. The material for this study was collected from the author's records from Josef-Kinderspital and from Mount Sinai Hospital, from the necropsy findings in infants who died of tuberculosis before six months of age (Koch (H.); Ghon, Kudlich, Winternitz), and from the postmortem records of cases reported as congenital tuberculosis. In all, there were 209 infants who died of tuberculosis before six months of age. Tuberculous meningitis was reported in 51 of these cases. The distribution of these 209 cases of lethal tuberculosis and 51 cases of tuberculous meningitis was as follows:

Age in months	*Cases of lethal tuberculosis*	*Cases of tuberculous meningitis*	*Percentage of lethal tuberculosis with tuberculous meningitis*
0–1	25	0	0
1–2	21	0	0
2–3	38	3	7.9
3–4	48	16	33.3
4–5	37	12	32.4
5–6	40	20	50.0
	209	51	

In the first two months, although there were 46 cases of lethal tuberculosis, there was not one case of tuberculous meningitis reported. In the third month, there were 38 cases of lethal tuberculosis of which 3 (7.9 per cent) were reported with tuberculous meningitis. Between the fourth and

[3] Personal communication from one of the authors.

sixth months, there were 125 cases of which 48 (38 per cent) had tuberculous meningitis. These figures are not meant to represent the exact relationship of tuberculous meningitis to lethal tuberculosis in the first six months, because the number of cases is too small. However, they do

TABLE 3

Incidence of tuberculous meningitis in cases of lethal tuberculosis in each year of childhood

SOURCE	TOTAL	AGE IN YEARS															
		0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	12–13	13–14	14–15	15–16
Josef-Kinderspital																	
Tuberculous meningitis	100	26	21	16	10	8	9	1	2	1	2	2	1	1			
Lethal tuberculosis	140	48	31	17	11	9	10	1	2	1	3	3	1	3			
Per cent of lethal tuberculosis with meningitis	70	54	70	94	91	89	90	70									
Mount Sinai Hospital																	
Tuberculous meningitis	302	55	64	54	39	20	18	14	15	8	5	2	5	3			
Lethal tuberculosis	344	70	77	61	40	23	18	16	15	9	5	2	5	3			
Per cent of lethal tuberculosis with meningitis	88	78	83	89	97	87	100	83	100	89	100						
Sea View Hospital																	
Tuberculous meningitis	43	5	14	8	2	1	2	1	2	1	0	0	1	1	3	1	1
Lethal tuberculosis	258	12	25	18	7	5	10	9	11	7	10	9	12	23	31	22	47
Per cent of lethal tuberculosis with meningitis	17	41	56	44	28	20	20	11	18	14	0	0	8	4	10	4	2
Koch (Wiener Kinderklinik)																	
Tuberculous meningitis	146	30	35	17	14	11	5	11	8	7	3	1	2	2			
Lethal tuberculosis	243	75	60	26	20	14	9	12	8	11	3	1	2	2			
Per cent of lethal tuberculosis with meningitis	60	40	58	65	70	78	55	91	100	63	100						
*Orosz**																	
Per cent of lethal tuberculosis with meningitis	?	60	72	74	78	78	72	68	52	52	48	40	30	18	22		

* In this study the percentage only as obtained from a graph, was available.

indicate that tuberculous meningitis does not occur before two months of age, that it is rare in the third month, and frequent thereafter.

In infants and children older than six months, the exact relationship of tuberculous meningitis to lethal tuberculosis is not definitely established, owing to the differences in results from the few available sources (table 3).

This is illustrated in the data from Mount Sinai and Sea View Hospitals, both in the same city and under the same director of pediatrics. At Mount Sinai Hospital, tuberculous meningitis occurred in 302 (88 per cent) out of 344 children dying of tuberculosis; while at Sea View hospital, there were only 38 (24 per cent) cases of meningitis in 158 cases of lethal tuberculosis. Of the cases between 5 and 12 years of age, there were 70 out of 73 (95 per cent) at Mount Sinai and only 8 out of 91 (9 per cent) at Sea View.

The explanation for these marked differences lies in the nature of the disease, the type of case admitted, and the duration of hospitalization. At Mount Sinai Hospital, only acutely or critically ill patients are admitted and those whose diagnosis is not certain. Cases of meningitis are accepted while those with other forms of tuberculosis are referred to Sea View Hospital immediately or after a short period of hospitalization. Under such conditions, the usual finding in children dying of tuberculosis at Mount Sinai is meningitis. At Sea View Hospital, it is rare for a patient to be admitted with tuberculous meningitis. Here, patients with chronic forms of tuberculosis are collected from the clinics and hospitals of New York City and kept until they improve or die. Death in these chronically ill patients usually occurs from their increasing cachexia and tuberculous progression, or, less commonly, from the advent of a late form of tuberculous meningitis. These factors of selection, and of duration of hospitalization, exist in varying degrees in different institutions throughout the world and determine the relationship of tuberculous meningitis to lethal tuberculosis in these various institutions.

Differences in the results from various sources (table 3) are seen not only in the percentage of lethal tuberculosis with meningitis, but also in the trend of this relationship from year to year. At Mount Sinai Hospital and Josef-Kinderspital, the percentage of lethal tuberculosis with meningitis is high in the first year, and rises in the second and third years to a maximum which is maintained throughout childhood. At Sea View Hospital, the percentage is high in the first three years and low afterward, especially at puberty when there is a marked increase in the number of cases of lethal tuberculosis without meningitis.

Similar differences in the trend of the relationship of tuberculous meningitis to lethal tuberculosis is seen in the data published by Koch and by Orosz (table 3). The data of Koch were taken from the records of the Wiener Kinderklinik from 1903 to 1911 and closely parallel the data from Josef-Kinderspital and Mount Sinai Hospital. The data of

Orosz, apparently from the Wiener Kinderklinik from 1912 to 1928, show a steady rise in the percentage of lethal tuberculosis with meningitis in the first four years to its highest level, where it remains for two years and then steadily drops, reaching a low level at puberty. These results are similar to those obtained in the study of vital statistics, such as Goetzl gives for Vienna from 1924 to 1926, or Abt and Watson for the United States from 1922 to 1926.

From the observations noted in tables 2 and 3, the trend of the relationship of tuberculous meningitis to lethal tuberculosis in the first three years of life is shown. Beginning with no tuberculous meningitis in the first two months, there is a small percentage of lethal tuberculosis with tuberculous meningitis in the third month followed by a sharp rise in the percentage to a high level in the fourth month. Afterward there is a rise in the percentage of lethal tuberculosis with meningitis in the remainder of the first year, through the second and third years and perhaps the fourth year, when the maximum seems to be reached. After the fourth year, our data are inadequate for determining the trend of the relationship of tuberculous meningitis to lethal tuberculosis.

PATHOGENESIS

It is well known that death from tuberculosis before three months of age is uncommon, owing to the slow development of tuberculosis from its inception. This slow development seems to be due, in part, to the relatively low rate of multiplication of the tubercle bacillus, and to the tendency to tubercle-formation or encapsulation. The speed of the tuberculous process is increased if the dosage is greater and the resistance is less (Roemer). When allergy develops, the tissue response is immediate and marked, and encapsulation occurs unless there is excess local tissue destruction, with rupture of the tuberculous material into the adjacent spaces.

The usual pathological findings in infants who die of tuberculosis before three months of age are pulmonary tuberculosis and generalized miliary tuberculosis. In many who die of tuberculosis during this age-period, only the lungs and their regional lymph nodes are macroscopically involved. In such cases, the lungs have an acute fulminating process, which may cause death in three to four weeks after onset, and other organs show no macroscopic lesions. Upon microscopic examination, minute fresh tubercles and necrotic areas containing tubercle bacilli may be found in various organs, especially in the liver and spleen. This

indicates that there was a tuberculous bacillaemia and that the infants died before macroscopic tubercles could develop. In infants who do not die so soon, tubercles appear in many organs, and a few isolated tubercles may also be found in the brain and meninges. Although tubercles of the brain and meninges have been found in infants of all ages, even in the still-born in congenital tuberculosis, the author knows of no undoubted case of tuberculous meningitis in infants who died of tuberculosis before two months of age. If life is prolonged to the third month, tuberculous meningitis may appear, for several cases have been reported at this age.

The apparent delay in the production of tuberculous meningitis is not due to the soil, which seems excellent (Cohn), but to the difficulty of getting enough free bacilli into the intermeningeal spaces. As far back as 1898, Péron recognized that tuberculous bacillaemia in itself is not enough to cause meningitis directly. He also stated specifically that tuberculous meningitis can be produced experimentally only by the subarachnoid route, a procedure previously employed by Martin. Subsequent workers (Armand-Delille; Fieandt) verified these conclusions, even in animals, which had first been repeatedly infected by the intravenous route (Simpson and Gloyne). Others (Austrian; Manwaring; Soper and Dworski) found that tuberculous meningitis might cause miliary tuberculosis, because several of their animals, following injections of tubercle bacilli into the subarachnoid space, developed disseminated tuberculosis as well as meningitis. In spite of these findings, the haematogenous route was commonly accepted as the usual portal of entry in man, largely because of the frequency with which meningitis was associated with miliary tuberculosis, and because of the perivascular and even intimal lesions in the cerebral vessels (Hektoen). However, it was recognized that extension from a local tuberculous process in the brain or spinal cord, in the skull, spine, or middle ear (Crowe), might also cause tuberculous meningitis. Some workers, like Kment, felt that tuberculous meningitis was caused by the spread of bacilli from a tubercle in the choroid plexus. Finally, Rich and McCordock tried to show that tuberculous meningitis can be caused only by the direct spread of a local focus into the ventricles or subarachnoid space. They found the focus, in most instances, to be a small soft tubercle in the brain or meninges, near the subarachnoid space or ventricles. In single instances, involvement of the choroid plexus and of the vertebrae was the source. They substantiated the fact that the haematogenous route in both the allergic and nonallergic animal can initially produce isolated tubercles only. A

diffuse meningitis may develop eventually if the conditions present favor the rupture of a tubercle into the subarachnoid space or ventricles.

While it is true that conditions in the experimental animal are not entirely the same as those in the human subject, there is evidence that the vascular route in man may also initially produce a few isolated tubercles in the brain and meninges but not a meningitis. Such evidence is found in cases of *congenital* tuberculosis in which the portal of entry is haematogenous, through the umbilical vein. In these cases, there is generalized miliary tuberculosis, occasionally with tubercles in the brain and meninges, but no evidence of meningitis. An example of such a case is a stillborn reported by Whitman and Greene, in which there were "occasional caseous tubercles in the floor of both lateral ventricles" and in the thalamus but no meningitis. Additional evidence is afforded by the fact that there is generalized miliary tuberculosis without meningitis in *acquired* tuberculosis. To this group may now be added virtually all the cases dying from tuberculosis in the first two months and most of those dying in the third month, when tuberculous meningitis begins to appear.

On the other hand, there is ample proof that tuberculous meningitis is caused by the direct extension from a local focus. This proof has been summarized by Rich and McCordock. They remind us of the occurrence of tuberculous meningitis without generalized miliary tuberculosis, of the differences in age between the brain lesions and the lesions elsewhere, of the finding of tuberculous foci that have ruptured into the subarachnoid space, and of the similarity of basal and vascular lesions in the brain of man and in experimental animals infected by the subarachnoid route.

What the conditions are that favor the rupture of a tubercle into the subarachnoid space are not entirely known. All that we are able to say at present is that tuberculous bacillaemia is a necessary antecedent in planting the seeds for tuberculous foci. If the seed is finally planted near enough to the subarachnoid space or ventricle; and if the conditions, perhaps of allergy and relative resistance of the host, become favorable for their development, and for the rupture of the focus into the subarachnoid space or ventricle, meningitis may occur.

Therefore, it is apparent that, if meningitis occurs, its onset is delayed, as in infants with pulmonary and miliary tuberculosis who linger on until meningitis finally develops and hastens their death. If meningitis does not occur, either the child died too soon or the local conditions necessary for depositing bacilli into the subarachnoid space are not favorable enough. The former is exemplified in a fulminating pulmonary tubercu-

losis in which death might occur even before macroscopic disseminated tubercles appear in other organs; the latter, by cases with well encapsulated or even calcified brain tubercles.

SUMMARY

1. An analysis was made of the age distribution of 445 cases of tuberculous meningitis among 742 children who died of tuberculosis at Josef-Kinderspital, Mount Sinai Hospital and Sea View Hospital. In addition, a similar analysis was made of approximately 3,000 cases of tuberculous meningitis reported in the literature in the past thirty years.

2. Of the total cases in childhood, there were 57 per cent in the first three years, 26 per cent in the next three years, and 17 per cent between six and twelve years of age. The greatest number of cases occurred between the ages of nine and fifteen months.

3. No undoubted case of tuberculous meningitis was reported in infants who died under two months of age of either acquired or congenital tuberculosis. There were a few cases of tuberculous meningitis in the third month. At this age, the percentage of cases of lethal tuberculosis with meningitis was low (7.9 per cent). After the third month, the incidence of tuberculous meningitis in infants who died of tuberculosis increased markedly, reaching 33 per cent in the fourth month and 50 per cent in the sixth month. The percentage gradually increased in older infants and reached its maximum (about 80 per cent) in the third and fourth years.

4. There were no cases of tuberculous meningitis in 68 cases of acute meningitis in infants below two months of age. About 90 per cent of these 68 cases were caused by the streptococcus, colon bacillus, pneumococcus, and meningococcus.

5. Additional data are presented to show that tuberculous bacillaemia is the precursor, but not the direct cause, of meningitis, which may eventually result from extension of a local tuberculous focus into the subarachnoid space or ventricles.

6. The incidence of tuberculous meningitis in lethal tuberculosis, as reported from various hospitals, depends largely on the type of tuberculous case admitted to these hospitals and on the duration of hospitalization.

The author is indebted to Professor Carl Sternberg for the use of his necropsy records of cases from the Josef-Kinderspital, Vienna.

BIBLIOGRAPHY

ABT AND WATSON: Handb. d. Kindertuberkulose, Engel & Pirquet, ii, 1229.
ARMAND-DELILLE, P. F.: Thèse de Paris, 1903.
AUSTRIAN, C. R.: Bull. Johns Hopkins Hosp., 1916, xxvii, 237.
BARRON, M.: Am. J. Med. Sc., 1918, clvi, 358.
BOSSELUT, F.: Thèse de Paris, 1888.
COHN, H.: Arch. Psychiat., 1932, xcviii, 451.
CROWE, S. J.: Arch. Otolaryng., 1930, xi, 537.
ENGEL, S.: Handb. Kindertuberkulose, Engel & Pirquet, i, 522.
FABRIS, S.: La Pediatria, 1924, xxxii, 199.
VON FIEANDT, H.: Arb. Path. Inst. Univ. Helsingfors, 1910–1911, iii, 235.
FOTHERGILL AND SWEET: J. Pediat., 1933, ii, 696.
GEIPEL, P.: Ztschr. Hyg. u. Infektionskr., 1906, liii, 1.
GERHARD, W. W.: Am. J. Med. Sc., 1834, xiii, 313; Med. Examiner 1840, iii, 293.
GHON, KUDLICH AND WINTERNITZ: Ztschr. Tuberk., 1925, xlii, 3 & 97.
GOETZL, A.: Handb. d. Kindertuberkulose, Engel & Pirquet, ii, 1362.
HARTWICH, A.: Virchow's Arch. path. Anat., 1922, ccxxxvii, 199.
HEKTOEN, L.: J. Exper. Med., 1896, i, 112.
HERBEN AND ASSERSON: Amer. Rev. Tuberc. 1925, xi, 184.
HOLT, E.: Am. J. Dis. Child., 1911, i, 26.
KINNEAR, W. L.: Lancet, 1925, ccviii, 19.
KMENT, H.: Tuberk. Biblioth., 1924, xiv.
KOCH, H.: Ztschr. Kinderhk., 1912–1913, v, 354; Ergebn. inn. Med., 1915, xiv, 99.
KOPLIK, H.: Arch. Ped., 1916, xxxiii, 481; Jour. Am. Med. Ass., 1907, xlviii, 1149.
LICHTHEIM: Deutsche med. Wchnschr., 1893, xix, 1186 & 1234.
LAFARCINADE, D. T.: Thèse Paris, 1906.
MANWARING, W. H.: J. Exper. Med., 1912, xv, 2.
MARTIN, L.: Compt. Rend. Soc. Biol., 1898, v, 273.
MCCLELLAND, H.: Canad. Med. Assoc. Jour., 1922, xii, 157.
MEYERS, A. E.: Am. J. Dis. Child., 1915, ix, 427.
NEAL, JACKSON AND APPELBAUM: Infections of the central nervous system, Williams & Wilkins, N. Y., 1932, xii, 397.
NEAL, J. B.: Jour. Am. Med. Assoc., 1924, lxxxii, 1429.
OROSZ, D.: Beitr. Klin. Tuberk., 1931–1932, lxxix, 163 & 173.
PAPAVOINE, M.: J. d. prog. des Sc. Méd., 1830, ii, 84.
PATERSON, D.: Practitioner, 1923, cx, 431.
PÉRON, A.: Arch. Gen. d. Méd., 1898, ii, 412 & 567.
PLISCHKE, W.: Arch. Kinderhk., 1930, lxxxix, 103.
QUINCKE, H.: Cong. innere Med., Wiesbaden, 1891, 321.
RICH AND MCCORDOCK: Bull. Johns Hopkins Hosp., 1933, lii, 5.
RILLIET AND BARTHEZ: Traité clinique et pratique des maladies des enfants, Paris, 1843, iii, 534.
ROEMER AND JOSEPH: Beitr. Klin. Tuberk., 1910, xvii, 289.
ROSENBLUM AND MAKLER: Arch. Ped., 1932, xlix, 667.
RUFZ: Cited by GERHARD, Med. Examiner, 1840, iii, 293.
SIEGEL, M.: Amer. Rev. Tuberc., 1934, xxix, 297.
SIMPSON AND GLOYNE: Tubercle, 1928, ix, 305.
SOPER AND DWORSKI: Amer. Rev. Tuberc., 1925, xi, 201.
STEINMEYER, W.: Virchow's Arch. path. Anat., 1914, ccxvi, 452.
VON WANGENHEIM, D.: Beitr. Klin. Tuberk., 1928, lxx, 670.
WHITMAN AND GREENE: Arch. Int. Med., 1922, xxix, 261.
WHYTT, R.: Observations on the dropsy in the brain, 1768.

SILICOSIS AND SILICO-TUBERCULOSIS CENSUS

Response of Silico-Tuberculosis to Treatment

A Preliminary Report[1]

DANIEL M. BRUMFIEL AND LEROY U. GARDNER

Actuated by a desire to get a fair idea of the distribution of silicosis and silico-tuberculosis in the United States, and also of the behavior of such patients when subjected to the treatment that prevails for uncomplicated tuberculosis, a preliminary survey has been carried on by mail during the past several months.

Letters of inquiry were sent to a selected and representative list of 128 sanatoria for tuberculosis asking for information and coöperation. The letters inquired merely as to the number of such cases that had been under observation and whether the staff of each institution which had such case records would care to coöperate in a more detailed study, should it prove feasible.

The results have been most gratifying. Of the 128 institutions addressed, more than 80 have replied. Thirty-five states of the Union are represented among the replies and the number of case records available has far exceeded our expectations.

The statistics from the different institutions varied from "never had a case" to "3.5% of all admissions." The widely varying local experience is well illustrated in the excerpts from two letters, both from the same state, which we take the liberty of quoting. The first, "I believe you will find that cases of this type in this section are few and far between except in those scattered areas where there are stone quarries;" the second, "Since my connection with the ———— Sanatorium, beginning in 1925, we have seen .... approximately 45 cases of silicosis and silico-tuberculosis. These patients have come from such trades as workers in the manufacture of fire brick, foundry workers, and tool grinders."

As to behavior under sanatorium treatment, the reports have been equally divergent. Some replies state that all patients have done poorly,

[1] From the Saranac Laboratory for the Study of Tuberculosis of the Edward L. Trudeau Foundation, Saranac Lake, New York.

others assert that many have done well and some have been discharged with their tuberculosis classified as quiescent or even arrested.

From the point of view of evaluating the response to treatment, we felt that as few as 100 accurate case records would throw much light on the subject and justify valuable inferences. Fortunately this number has already been exceeded, the replies indicating that several hundred case records are on file. Each additional case will be welcomed for the added significance which it will render to the generalization.

From the point of view of estimating the occurrence and distribution, it is obviously important that we have reports on as many cases as possible from sanatoria, clinics, hospitals, industrial surgeons, and private physicians everywhere. If a census is to be worth-while, it must be as complete as possible. In order to bring this about, the Director of the Saranac Laboratory for the Study of Tuberculosis is willing to have that institution serve as a central, confidential, registry of all such cases.

We are publishing this preliminary report in the hope that it may attract attention to this condition and that from it we may recruit volunteer contributors of the necessary data.

For the guidance of those contributors who have the time and interest sufficient to make detailed reports, we suggest the following points as being important to our study.

Age and nationality of patient

Occupational history: Chronological list of time spent in all occupations, whether hazardous or not. Regarding known hazards, specific information as to operations engaged in, working conditions, and, if possible, nature of materials used, as well as length of exposure; the industry, such as mining, foundry, machine shop; occupation within the industry, such as driller, moulder, tool grinder.

Past medical: Significant items, such as respiratory diseases, syphilis, and infections predisposing to cardiovascular damage.

General clinical condition on admission, including symptoms and signs. Time of onset of symptoms in relation to length of exposure, and lapse of time since exposure.

X-ray: Type of pneumonoconiosis, and *stage* of development,
Stage of tuberculosis and *type.*

Sputum: Direct examination, culture or animal inoculation.

Clinical course under observation

Special treatment: Pneumothorax, thoracic surgery, etc.

Length of time under observation
Condition upon discharge
Follow-up, after discharge, when known

To those who are not in a position to make detailed reports, we wish to say that any report, no matter how brief, even to a mere registering of such and such cases, will be welcomed.

In order to preserve the traditions of professional confidence all letters and reports received are given a number and thenceforth referred to in our compilations by state and number only. Furthermore, in order to doubly safeguard against any leaks of information, in these times when many of these cases have medico-legal significance, we ask the contributors to designate their cases by number or symbol.

We wish particularly to thank the many sanatorium directors and others whose willing coöperation has brought this investigation to its present stage. Also, we express our appreciation in advance to all those who may volunteer assistance as a result of this general appeal.

THE PLACE OF THE LABORATORY IN THE SANATORIUM[1]

HENRY STUART WILLIS

Two recent experiences prompt the discussion of this subject before this society. One of these was a visit to a large public sanatorium where the so called laboratory was entirely unworthy of the name, and the other was Dr. McSweeney's report last year before this body on behalf of the Committee on Sanatorium Standards. This report indicated that many sanatoria fail to appreciate the value of the laboratory and to utilize it to advantage.

The story is familiar to all of us how Trudeau, when he heard first of Koch's discovery of the tubercle bacillus, set about to learn the technique of microscopic search for this bacterium. He made a visit to Prudden's laboratory, where he was provided with a microscope, a specimen, and a few directions as to procedure. His own words describe his difficulties and his final triumph.

> During the first three days I worked unremittingly and stained my fingers, my clothes, even my shoes; and if I stained the bacillus I decolorized the specimen either too much or too little, so that the germ remained invisible under the microscope. . . . . At first Dr. Prudden took little notice of me . . . . but after several days had passed . . . . he sat down beside me and pointed out to me where my mistakes had been. At last I succeeded, and remained that day until late, repeating my attempts on different specimens . . . . until I was quite sure I could bring out the bacillus on the slides.

This quotation emphasizes well the fact that the laboratory and laboratory procedure are developments of relatively recent years. So is the sanatorium for that matter, but it is now fully realized that the sanatorium and the sanatorium laboratory have not grown apace. In the not far distant past, the emphasis was all upon clinical contact, and at a time when laboratory and X-ray examinations were unheard of or were highly exceptional. Later, and in some places even now, a single examination of the sputum, made some time during the course of the treat-

[1] From the Wm. H. Maybury Sanatorium, Northville, Michigan.

ment, was deemed sufficient, and gave great comfort to the physician and the patient when it was negative. Now, with clinical history and clinical examination still highly valuable and as necessary as ever, failure to utilize the laboratory facilities and the X-ray in the diagnosis and management of the case of tuberculosis, might properly be considered a species of criminal negligence.

The chief function of the laboratory is to aid the clinician in the diagnosis and management of the patient. This function may be utilized much or little, and the laboratory may be of very great or very limited value to the clinician in proportion as the latter uses intelligence and judgment in determining the time for observations and the type of material to be studied and the general scope of the work,—all in proportion to the calibre and training of the laboratory personnel. This function can be realized only if there exists an attitude of coöperation and understanding between the clinic and the laboratory. To initiate and maintain this attitude the clinician should furnish the laboratory with a description of the material to be examined, explicit data as to just what is wanted, and a statement of the clinical diagnosis, definite or presumptive. Thus he will provide the laboratory staff with an intelligent interest in the question at issue. In turn, the laboratory staff may be expected to contribute ready and intelligent work and may not infrequently offer helpful suggestion. Frequent contact between the clinician and the laboratory worker will go far toward elucidation of many of the problems that puzzle each.

The laboratory *may* carry on an almost infinite variety of tests and examinations of the secretions, excretions and tissues of the body—some of these useful, some serving only as tinsel or ruffles. It *should* be prepared to perform any test, analysis or examination required of a well-ordered laboratory in a first-class hospital. These requirements fall logically into the following categories:

1: Bacteriological: The clinician has the right to expect, on request, a detailed examination for bacteria of sputum, urine, cerebrospinal fluid, pleural, ascitic or pericardial fluid, of blood, of smears of material from the nose, throat, eye, ear, genitourinary system or sinuses, of pieces of tissue, pneumoliths or other unusual specimens,—the examination to be microscopic, cultural, biological, or histological, as indicated by the nature of the clinician's request. This should include search for parasites, particularly in the blood and stools.

2: Haematological: It may be reasonably expected of the laboratory that any of the ordinary haematological examinations should be obtainable. Such examinations should be routine on the admission of the patient and should be available at any time thereafter when requested.

3: Urine Analysis: It goes without saying that urinalysis should be made routinely at admission and at intervals thereafter.

4: Anatomical and Histological: It is trite to mention the value and the need of the autopsy in medicine. In the sanatorium the autopsy will often elucidate and clarify the diagnosis, stimulate clinical and pathological interest, and step up clinical observation and procedure. Ideally the pathologist, certainly a highly desirable if not absolutely necessary officer in the sanatorium, should have charge of the laboratory; should be equipped to perform autopsies, and to carry the tissues, whether from autopsy, biopsy or experimental animal, through to examination, description and diagnosis in the microscope. He should be skilled alike in clinical and pathological concepts, both of which he should be able to synthesize and correlate.

5: Chemical: The laboratory should be able to furnish the clinician requested information as to the chemistry of the blood, cerebrospinal fluid, serous fluids or urine, and should, as well, perform, on requisition, renal function tests, basal-metabolic rate determinations, Van Den Bergh tests, etc.

6: Serological: The laboratory routine should include a Wassermann or comparable test on the blood of each patient on admission.

7: Experimental: Our knowledge of the nature, diagnosis and treatment of tuberculosis has been advanced enormously in the last two decades. This progress has been brought about through the careful clinical, roentgenological, pathological and experimental observations of many people. The sanatorium laboratory has been and should be an important unit in the antituberculosis scheme, in which much gleaning of fact and formulation of concept takes place. In addition to being the seat of the routine and investigative work of the laboratory director and his staff, the laboratory should offer a "hide-out" for the clinician when, from time to time, he might carry on studies either alone or jointly with other

members of the clinical or laboratory staff. It should be a focal point for investigation.

8: Miscellaneous: In addition to these functions the laboratory should be responsible for the conduct of certain other miscellaneous tests and examinations, such as frequent analyses of the sanatorium milk and water supply, the routine throat culture studies of children newly admitted but held in quarantine against the importation of acute infectious diseases of childhood, the preparation of solutions, tuberculin, etc.

It is agreed by all that these functions are desirable, but the objection may be raised to such a laboratory layout on the score that it is too costly, or unnecessarily elaborate, or that it does not separate the desirable procedure from the absolutely necessary. It is obvious that certain of these contentions are true. What, then, are the minimal requirements for the sanatorium laboratory which are necessary and without which the sanatorium falls short of its obligation to the patient and to society?

These absolute requirements are few and simple. They are, first and most important, dependable and thorough search for tubercle bacilli in the body fluids, secretions and tissues; second, blood and urine analysis and study of gastrointestinal contents; and third, serological examination. It requires little comment to indicate the very considerable worth of these procedures and their clinical value, and it would be boresome to labor the question at any length.

The two last-named essentials may be disposed of in a word. The necessity of blood, urine and (often) stool analysis when the patient is admitted and at any indicated time afterward is recognized by all. The occasion arises not infrequently when the clinician should know the degree of anaemia of a given patient, the number and differential count of the white blood cells, or the content of the urine; when culture of the blood or urine may clear up the diagnosis of a complication or an intercurrent infection; when examination of the gastric contents or stool may contribute facts of value. An admission Wassermann (or equivalent) examination should be made on each patient. Such examinations are readily available in either public or private laboratories, and it is unimportant whether the tests are done in the sanatorium laboratory or elsewhere.

Whether the sanatorium physician should treat whatever syphilis exists in his tuberculous patients is a matter that is still debatable al-

though it has been shown that the tuberculous patient with syphilis tends to handle his tuberculosis less well than the one not so diseased. Obviously, serological examination should be made at fairly frequent intervals if the patient is receiving antisyphilitic treatment.

In discussing the search for tubercle bacilli as one of the essential laboratory services, let us confine our attention chiefly to the sputum. The time has passed when casual search for tubercle bacilli is made by a poorly trained ex-patient who uses indiscriminately for smear whatever portion of the specimen that might adhere to the toothpick, hatpin or similar implement which he uses to dip blindly into a deep, often colored, narrow-neck container.

The detection of tubercle bacilli means too much in the diagnosis and treatment of the patient to allow less than repeated, prolonged, conscientious search of properly selected, prepared and stained material. How often have we seen the appearance of a few tubercle bacilli in the sputum of a patient who had been negative for a considerable time presage retrogression of his disease, indicate the importance or desirability of closer clinical and laboratory check, or, if confirmed or continuous, point to the need of further collapse of the diseased area!

How important it is to search especially the small, whitish, granular bits of the sputum with care and at frequent intervals when the patient, long at rest, begins to increase his physical activity; while the pneumothorax is being discontinued; during the period while the diaphragm resumes function as the effect of the phrenic crushing begins to wane, or as the patient with thoracoplasty prepares himself physically for subsequent discharge and occupation!

The occasional, unexpected positive sputum is most disturbing and, in a properly conducted laboratory, is rarely accidental or without significance. This, of course, is not to say that every instance of positive sputum indicates impending disaster but it is emphatically to say that frequent, careful examination of the sputum is one of the most helpful and reliable indicators that the clinician may employ. And this is a plea for its more liberal use.

Likewise the significance of the repeatedly *negative* sputum is considerable, as Pinner and Werner have recently clearly indicated when they showed that the patient with pulmonary tuberculosis sheds tubercle bacilli in his sputum at some stage of his disease in 99 per cent of cases. If this be so, then the clinician is doubly fortified in the management of the patient when, along with clinical and roentgenological evidence of

clearing disease, he is aware confidently that the lesion is no longer emitting detectable tubercle bacilli.

Ideas of adequacy in sputum examination vary with different people. If upon admission, single specimens of sputum are examined daily for the first two days, by direct smear, and one or both of them are found to contain bacilli, the diagnosis is confirmed and a helpful suggestion as to the need of some form of collapse therapy is at the clinician's hand. If they are negative, the clinician desires still to know whether the lesion is shedding bacilli in small numbers. His routine scheme then requires the examination of two consecutive 24 hour specimens by direct smear, and, if negative in this examination, by concentration and culture or guinea pig inoculation. He directs that thereafter a 24-hour specimen of the patient's sputum be examined routinely by direct smear every six weeks. If the sputum, previously negative, is positive on routine examination, the examination (and culture if negative) of at least three consecutive 24-hour specimens follows routinely. Further, the laboratory service is at the clinician's disposal for more frequent or varied examinations if he requires such.

The question arises logically as to whether the methods of concentration, culture and guinea-pig inoculation add sufficiently to the clinician's data to justify their use. We are familiar with the many and varying claims that have been made in this connection. Experience shows that, in general, concentration methods will add about 5 per cent to the number of positive cases over direct-smear examination, and that culture and guinea-pig inoculation will add roughly another 15 to 20 per cent.

In our laboratory last year 521 examinations by culture were made of specimens negative on concentration, with the result that 101 additional positives were found, that is, culture added 19.3 per cent.

In keeping with the experience in numerous other sanatoria, we have come to rely increasingly upon culture in the study of our cases, for the reasons that it yields a high incidence of accuracy; it is rapid in its results as compared to animal inoculation, and is much less expensive than the latter. Obviously, it is well to employ both methods if possible.

But the answer to the query just raised as to the justification of these various manoeuvres is this,—that the use of any method which adds worth-while information to the case record is justifiable if it is reasonably practical. And all requisite tests can be done in a laboratory which averages one worker in the laboratory personnel to every 100 patients.

Little has been said here concerning the examination of the body prod-

ucts other than sputum. It scarcely need be pointed out that, in all of these, attentive search for bacilli, by whatever method, will add to the clinician's armamentarium.

These laboratory services represent the minimal requirements of the sanatorium, if the latter is to treat tuberculous patients adequately and is to give them the best. It is difficult to see in what way the sanatorium may justify its action if it proceeds on a lower basis than this minimum.

AN ATTEMPT TO "DESENSITIZE" TUBERCULOUS GUINEA PIGS WITH DEAD VACCINE AND PRODUCTS OF THE TUBERCLE BACILLUS[1]

C. L. DERICK, E. A. G. BRANCH AND M. P. CRANE

In their studies on rheumatic fever Swift and his co-workers were able to produce in rabbits a hypersensitive condition to streptococci. This state of hypersensitiveness resembled in many respects that found in tuberculosis. These workers were also able to change the animals from this hypersensitive state to one of immunity or hyposensitiveness by appropriate treatments with living and killed streptococcus vaccines. The intravenous route was found to be much the most efficacious for this purpose. This work is well summarized in their paper entitled *Intravenous Vaccination with Streptococci in Rheumatic Fever* (1). Rich, Jennings and Downing (2), working with *P. aviseptica* and pneumococcus, have obtained similar results.

In view of the suggestive similarity of the state of hypersensitiveness to streptococcus and to the tubercle bacillus in animals, the ease with which an animal hypersensitive to streptococcus can be rendered immune and the marked increase of resistance to reinfection which the immune animals show as compared to the hypersensitive ones, an attempt has been made to alter the state of sensitiveness of guinea pigs with active tuberculosis. At the time, it was realized that the two species of animals (rabbits and guinea pigs) have far different immunological reactions particularly in their response to hypersensitive phenomena.

The purpose of these experiments was not only to determine whether the degree of hypersensitiveness could be reduced, as judged by repeated tuberculin skin tests, but also to determine whether such a change, should it be accomplished, would influence the course and duration of the disease. Similar experiments have been carried out by Weinzirl (3) and collaborators during the past few years. These workers have used various antigens in their work and claim the best results with whole organisms which were killed and treated with ether and, more recently, with "natu-

[1] From the Departments of Medicine and Pathology, Harvard Medical School, and the Medical Service, Peter Bent Brigham Hospital, Boston, Massachusetts.

ral tuberculin" prepared by repeatedly freezing and thawing the bacilli before extracting the tuberculin. Rothschild and his co-workers (4) injected guinea pigs with a strain of tubercle bacillus, R1, which was of low virulence, desensitized the animals with tuberculin (O.T.), and were then able to keep them desensitized, as judged by repeated skin tests, during a following period of reinfection with virulent tubercle bacilli. However, their work is hardly comparable to the present studies since the infecting strain against which they obtained desensitization was of such low virulence. DeSavitsch, Treverron, Black and Lewis (5) treated tuberculous animals with viosterol and tuberculin combined, and found that the treated animals lived longer than the untreated controls, showed less extensive macroscopic tuberculous involvement and a markedly diminished cutaneous response to tuberculin.

Several workers, among others Petroff (6), have treated active tuberculosis in human beings with various antigens from the tubercle bacillus, but no attempt has been made to abstract this literature.

METHODS

The tubercle bacillus, used both for infecting the animals and in the preparation of the vaccines or fractions thereof, was the human strain H37. The infecting dose was 1,000 organisms from a young glycerine-egg culture, emulsified in 0.5 cc. physiological salt solution, and given subcutaneously over the belly.

The vaccines used were prepared from one-month-old cultures on Proskauer's synthetic fluid medium. The heat-killed vaccine was made by boiling an emulsion for 20 minutes. For the formalinized vaccine the organisms were kept in 0.2 per cent formalin in salt solution for upward of a month; subsequent dilutions were made with salt solution. Each vaccine was tested for sterility before use on 2 guinea pigs. None of these developed tuberculosis. The bacillary emulsion (B. E.) was made in the standard manner. The protein fraction used was prepared by extracting ground-up dried organisms with faintly alkaline salt solution, precipitating with acetic acid, drying the precipitate and redissolving in alkaline salt solution.

The tuberculin used consisted of a two-month-old synthetic broth culture of H37 passed through a Berkfeld-V filter. The culture had been concentrated during growth in the incubator at 37°C. to approximately a quarter of its original volume.

EXPERIMENTAL

1. Vaccination with Heat-Killed Tubercle Bacilli and with Tuberculoprotein

On October 15, 1929, 80 guinea pigs, which had been found previously to be skin-test-negative to 0.1 cc. of 5 per cent tuberculin intracutaneously, were infected subcutaneously with 1,000 tubercle bacilli. In the following three weeks 9 animals died of intercurrent pulmonary infections. Intracutaneous skin tests with 0.1 cc. of 5 per cent tuberculin were repeated November 6, at which time only 11 guinea pigs were found to give a strongly positive response. Thirty more guinea pigs showed a strongly positive reaction when retested one week later. All surviving healthy guinea pigs, 65 in number, were retested, November 19, at which time all showed a definite reaction. They were then divided into 5 groups; each group contained 9 ++++ reactors, one ++ reactor and 3 + reactors. An attempt was made also to divide the animals by weight. The original weights had varied from 350 to 670 gm., the majority being between 400 and 500 gm. Group A was kept as controls, group B was inoculated intravenously with heat-killed tubercle bacilli, and group C intravenously with tuberculoprotein; groups D and E were injected subcutaneously with vaccine and tuberculoprotein respectively.

Treatment was initiated November 19, thirty-four days after the infecting dose. All treated animals received injections on four successive days followed by an interval of four days' rest. Three series of such injections were completed by December 11. All animals were skin-tested, December 16, with 0.1 cc. amounts of 5 per cent tuberculin and were all found to be markedly hypersensitive. Two further vaccine treatments were given December 18 and 19. Both vaccines were administered in gradually increasing amounts. The individual dose of nucleoprotein ranged from 0.001 to 2.0 mgm.; that of heat-killed tubercle bacilli from 10,000 to 1,500 million organisms. As the treated guinea pigs had lost considerably more weight than had those in the control group A, further vaccinations were discontinued until January 29, 1930, at which time all surviving guinea pigs were skin-tested with 0.1 cc. of 1:10,000 dilution of tuberculin. The members of groups D and E, which showed a ++ reaction or greater, were given four further series of treatments spaced as previously. Dosages for these treatments, 0.05 mgm. tuberculoprotein and 10,000,000 tubercle bacilli, were kept constant, since undoubtedly excessive amounts had been used before.

All guinea pigs were autopsied soon after death. Animals, dying just

previous to or soon after treatment was started, showed tuberculosis at the site of injection and of the regional lymph nodes and spleen.

The first death from generalized tuberculosis occurred 90 days after the time of infection. All animals that died within this limit, mostly of intercurrent infections, such as streptococcus pleurisy or pneumonia, are excluded from further consideration. The mortality in the intravenously vaccinated groups B and C was so great as to render these groups valueless. Either this route of inoculation in tuberculous guinea pigs is too toxic *per se* in the doses used, or else it lowers the animals' resistance to secondary infections.

TABLE 1

Skin tests with 1 : 10,000 dilution of tuberculin

CONTROLS (GROUP A)			SUBCUTANEOUS HEAT-KILLED (GROUP D)			SUBCUTANEOUS TUBERCULOPROTEIN (GROUP E)		
Guinea-pig number	January 29	March 3	Guinea-pig number	January 29	March 3	Guinea-pig number	January 29	March 3
33	++++	++++	31	++++	++	62	+++	+
36	++++	++++	74	++	±	65	++	±
38	++	++++	76	+	±	91	++	±
39	++	Dead (tbc.)	79	0	0	92	++	±
41	++++	++++	85	+	0	99	++++	++
44	++	++	86	+	0	101	±	Dead (tbc.)
61	++++	0 (sick)	88	0	0	102	++	++
						104	0	Dead (tbc.)
						105	++++	+++

All animals showed a strongly positive skin response to 5 per cent tuberculin when tested on December 16, as noted above, and again when retested on January 13, 1930. In view of this and the fact that all animals, including the controls lost weight following the tests it was decided to repeat them using a more dilute tuberculin.

This was done on January 29, 1930, when 0.1 cc. amounts of 1:10,000 dilution were used. The results are shown in table 1.

It will be noted that all control animals reacted either very strongly or moderately so, whereas a majority of the animals in both treated groups showed only a moderate reaction or none at all.

Following the further treatment of sensitive animals, as noted above, all were retested with dilute tuberculin, March 3, 1930. The results are included in table 1. There is definite evidence of further desensitization.

It would seem, therefore, that it is possible to lessen considerably the degree of skin sensitiveness to tuberculin in guinea pigs by the subcutaneous use of heat-killed vaccine and to a lesser degree with tuberculoprotein.

Duration of Life

As is usual in such experiments, there was considerable variation in the duration of life of animals in each group. Though all animals showed the presence of more or less tuberculosis at autopsy this was not the cause of death in several instances. Table 2 shows the duration of life, the cause of death and the amount of tuberculosis in the individual animals.

It will be noted that the average duration of life of the control animals was 148 days while that of the "tuberculoprotein" and heat-killed vaccine-treated animals was 156 and 201 days respectively. There was not only a greater average duration of life in the group-D animals, but also a smaller percentage in this group with sufficient tuberculosis to act as the cause of death. Such findings were not so for the animals in group E.

An analysis of tables 1 and 2 shows that in nearly all instances the animals which lived longest had shown the mildest responses to tuberculin. However, since several animals that were apparently healthy when tested and were only mildly sensitive died earlier than others that were much more sensitive, we do not feel that the tuberculin test was of great prognostic significance.

2. Vaccination with Formol-Killed Vaccine and Bacillary Emulsion

The previous experiment seemed to show that heat-killed tubercle bacilli not only desensitized tuberculous guinea pigs but also prolonged their life. It was then decided to determine the value of formol-killed vaccine and bacillary emulsion when given by the subcutaneous route.

On April 26, 1930, 60 guinea pigs were inoculated subcutaneously with 1,000 living H37 tubercle bacilli. Skin tests, June 5, with 2.0 per cent tuberculin showed all animals to be sensitive. They were divided into three groups of 17 animals each. One group was kept as controls. The other two were vaccinated either with formol-killed vaccine or with Koch's bacillary emulsion. Treatment was started June 7, with 100,000 organisms and 0.000,5 mgm. emulsion, respectively. Fourteen treatments in gradually increasing amounts were given by June 30; the final doses being 100,000,000 organisms and 1.0 mgm. emulsion. After in-

TABLE 2

Duration of life, amount of tuberculosis and cause of death

CONTROLS (GROUP A)				SUBCUTANEOUS HEAT-KILLED (GROUP D)				SUBCUTANEOUS TUBERCULOPROTEIN (GROUP E)			
Guinea-pig number	Days of life	Cause of death	Degree of tuberculosis	Guinea-pig number	Days of life	Cause of death	Degree of tuberculosis	Guinea-pig number	Days of life	Cause of death	Degree of tuberculosis
40	92	Tuberculosis	+++	78	94	Tuberculosis	+++	93	90	Tuberculosis	+++
59	92	Tuberculosis	+++	88	162	Pneumonia	++	63	94	Unknown	++
43	100	Tuberculosis	+++	31	184	Tuberculous meningitis?	++	100	94	Pneumonia	++
58	105	Tuberculosis	+++	76	185	Tuberculosis	++++	104	115	Tuberculous meningitis	+++
42	108	Unknown	++	74	187	Tuberculosis	+++	101	137	Tuberculosis	++++
39	132	Tuberculosis	++++	79	209	Unknown	++	91	160	Tuberculosis	+++
41	146	Tuberculosis	++++	86	288	Tuberculosis	++++	62	168	Tuberculosis	+++
36	157	Unknown	++	85	295	Tuberculosis	++++	105	170	Tuberculosis	++++
33	162	Tuberculosis	++++					99	184	Tuberculosis	++++
61	169	Tuberculosis	++++					92	187	Tuberculosis	+++
38	216	Tuberculosis	+++					65	204	Pericarditis	+
44	300	Tuberculosis	++++					102	255	Tuberculosis	+++
Average....	148				201				156		

tervals of 5 and 10 weeks the surviving animals were skin-tested with 1:10,000 dilution of tuberculin. The results are shown in table 3.

There is some evidence of desensitization in both treated groups. However, the significance of this is in doubt, since several of the animals that failed to react were obviously sick and died early.

TABLE 3

Skin tests with 1:10,000 dilution of tuberculin

CONTROLS (GROUP A)			SUBCUTANEOUS FORMOL KILLED (GROUP B)			SUBCUTANEOUS BACILLARY EMULSION (GROUP C)		
Guinea-pig number	August 5	September 10	Guinea-pig number	August 5	September 10	Guinea-pig number	August 5	September 10
109	0	0	106	+	Dead	118	0	Dead
122	+++	++	113	++	Dead	119	+	++
124	++++	+++	114	++	++	120	++	+
125	+++	+++	130	++	++	126	0	+
138	+++	++	134	++	+	127	±	±
141	++++	++++	145	+++	?	128	+	Dead
154	++	++++	161	++	+++	129	+++	+++
156	++	0	170	0	0	146	+++	0
181	±	++	172	0	Dead	147	++	±
183	++	++	174	0	?	148	0	+
						150	0 (sick)	Dead
						151	+++	++
						152	+	0 (sick)
						164	0 (sick)	Dead
						165	0 (sick)	Dead
						185	++	0

Duration of Life

As in the previous experiment the duration of life, cause of death and amount of tuberculosis found in the individual animals is shown in table 4.

A glance at table 4 reveals that the average duration of life was greater in the control than in either of the treated groups. Again, it shows that nearly all the animals treated with formol-killed vaccine died from widespread tuberculosis. This is not equally true of the group vaccinated with bacillary emulsion, though the differences when compared with the control group are not great. Hence, we can only conclude that, for the purposes for which they were used, these antigens were valueless.

An analysis of all control animals in both experiments showed that

TABLE 4

Duration of life, amount of tuberculosis and cause of death

CONTROLS (GROUP A)				SUBCUTANEOUS FORMOL-KILLED (GROUP B)				SUBCUTANEOUS BACILLARY EMULSION (GROUP C)			
Guinea-pig number	Days of life	Cause of death	Degree of tuber-culosis	Guinea-pig number	Days of life	Cause of death	Degree of tuber-culosis	Guinea-pig number	Days of life	Cause of death	Degree of tuber-culosis
184	100	Tuberculosis	++++	115	99	Tuberculosis	++++	142	95	Tuberculosis	++++
109	146	Tuberculosis	++++	144	101	Tuberculosis	+++	150	105	Tuberculosis	++++
141	169	Tuberculosis	+++	172	108	Tuberculosis	++++	118	107	Pneumonia	±
156	170	Tuberculosis	++++	106	116	Tuberculosis	++++	164	115	Tuberculosis	++++
122	186	Tuberculosis	+++	113	122	Tuberculosis	++++	165	122	Tuberculosis	+++
183	195	Unknown	+	170	148	Tuberculosis	++++	128	126	Peritonitis	±
138	197	Tuberculosis	++++	174	177	Tuberculosis	++++	152	143	Tuberculosis	++++
124	206	Tuberculosis	++++	161	181	Tuberculosis	++++	185	157	Tuberculosis	++++
154	228	Pneumonia	+	145	196	Tuberculosis	++++	146	157	Tuberculosis	++++
125	230	Tuberculosis	++++	114	213	Tuberculosis	++++	120	175	Pneumonia	++
181	232	Unknown	+	134	227	Tuberculosis	+++	147	178	Pneumonia	+
				130	230	Liver atrophy?	±	119	197	Tuberculosis	++++
								126	226	Unknown	±
								129	232	Unknown	++
								148	232	Tuberculosis	++++
								127	312	Pneumonia	±
								151	360	Unknown	±
Average...	187				160				179		

there was no relation between the body weight at the time of infection and later resistance to tuberculosis.

3. Comparative Effects of Intracutaneous Inoculation of Human Beings with Unheated Tuberculin and Heat-Killed Tubercle-Bacillus Vaccine

During the course of this work skin tests were done on several patients as well as ourselves. The test doses used were 0.1 cc. of a 1:100,000 dilution of unheated tuberculin and 0.1 cc. of an emulsion containing 1,000,000 heat-killed tubercle bacilli per cubic centimetre.

One of us (C.L.D.) reacted violently to the tuberculin in 24 hours, but only a slight reaction was noted at the site of the injected vaccine until 10 days after. This latter then proceeded to become inflamed. It ruptured finally and drained for a period of two weeks; then healed, leaving a small white scar. This result would appear to be of great importance if one contemplates using whole tubercle bacilli for purposes of vaccination. Since any attempt to increase dosage should be based on the reaction to the previous inoculation, there should be a considerable interval between treatments. Also, the initial inoculation of whole organisms should be much smaller. We anticipated neither so marked a response to a dose of this size (100,000 organisms) nor such a delay in its occurrence. Another of us (A. B.) did not react to either of the above dilutions. Such findings make one more doubtful of the clinical value of the tuberculin test since the former individual has never had active tuberculosis while the latter individual has had.

DISCUSSION

As a method of therapy in experimental tuberculosis that of active specific desensitization has seemed worthy of trial. Although it cannot be denied from Menkin's (7) work that an acute inflammatory reaction *per se* will tend to localize an infection, the allergic reaction in tuberculosis is so often accompanied by a massive reaction, that is, extensive necrosis of tissue, that conceivably spread rather than localization may well result. Rothschild and his collaborators (4) have shown that a considerable degree of immunity may be developed in animals that become skin-test-negative and such a condition would seem ideal. It has been observed by Kaminsky (8) that in patients with pulmonary tuberculosis a diminishing tuberculin reaction is associated usually with decreasing activity of the infection and a continued strongly positive reaction is indicative usually of persisting activity.

In the above experiments we have used four antigens for treatment; namely, heat-killed and formol-killed tubercle bacilli, Koch's bacillary emulsion and a protein fraction from the tubercle bacillus. By using quantitative skin tests we have obtained some evidence of desensitization by the use of heat-killed vaccine but not by the use of the other antigens. A substantial prolongation of life followed the use of heat-killed vaccine only, although in the series receiving the bacillary emulsion several animals showed little or no tuberculosis at the time of death. It must not, however, be assumed that all animals with a negative skin test outlived the others or that those with a strongly positive test died earliest, as this was by no means the case.

We believe that dosage may be an important factor, and this is very difficult to graduate, since there may be a delayed response following the use of whole bacterial vaccine in particular. The intravenous method of inoculation in the doses used proved too severe and had to be discontinued. None of the antigens used can be considered ideal, though heat-killed vaccine seems to have very definite value. This work was carried out before the suggestive work of Seibert (9) on the antigenic value of the protein fraction of tubercle bacillus appeared. It would be of interest to repeat the experiments, using tuberculoprotein prepared according to Seibert's method as the antigen.

In common with other workers we have found that it is much more difficult to diminish the hypersensitive state of animals when this state is due to infection with the tubercle bacillus than when due to other organisms such as streptococcus; this in spite of the fact that every attempt was made to keep the latter animals hypersensitive by repeated injections of living organisms or the subcutaneous presence of infected agar foci. An explanation of these differences is not forthcoming at present.

Whether any satisfactory antigen for active desensitization can be found remains to be determined. One may try passive desensitization, combinations of both the active and passive methods or some form of nonspecific therapy of the nature of enzymes or chemotherapeutic agents.

SUMMARY

1. Subcutaneous vaccination of tuberculous guinea pigs with heat-killed tubercle bacilli has resulted in quantitative diminution of the intracutaneous tuberculin reaction and a prolongation of life over control animals.

2. Intravenous inoculation has proved too fatal.

3. No substantial results were obtained with formol-killed bacilli, Koch's bacillary emulsion or the acetic-acid precipitable protein fraction.

4. The striking differences in the reactions of a sensitive human adult to an intracutaneous inoculation of unheated tuberculin and killed-tubercle-bacillus vaccine are described.

BIBLIOGRAPHY

(1) Swift, H. F., Hitchcock, C. H., Derick, C. L., and McEwen, C.: Am. J. Med. Sci., 1931, clxxxi, 1.

(2) Rich, A. R., Jennings, F. B., Jr., and Downing, L. M.: Bull. Johns Hopkins Hosp., 1933, liii, 172.

(3) Weinzirl, J., and Bohart, R. M.: Amer. Rev. Tuberc., 1931, xxiii, 393.
Weinzirl, J., and Weiser, R. S.: Tubercle, February, 1934, 210.

(4) Rothschild, H., Friedenwald, J. S., and Bernstein, C.: Bull. Johns Hopkins Hosp., 1934, liv, 232.

(5) DeSavitsch, E. C., Treverron, V. E., Black, W. C., and Lewis, R. C.: Amer. Rev. Tuberc., 1933, xxviii, 699.

(6) Petroff, S. A.: Personal communication.

(7) Menkin, V.: Arch. Path., 1931, xii, 802.

(8) Kaminsky, K.: Personal Communication.

(9) Seibert, F. B.: Jour. Inf. Dis., 1932, li, 383.

EPIDEMIOLOGICAL ASPECTS OF SILICOSIS AND TUBERCULOSIS[1,2]

ALTON S. POPE AND DAVID ZACKS

The unique rôle of silica dust in the production of certain types of pneumonoconiosis has long been recognized, and the association of tuberculosis and silicosis in workers exposed to such dust for long periods is too well known to warrant any detailed discussion here. It is the purpose of this paper to point out some of the quantitative aspects of the problem, as determined in a group of some 2,600 workers in the granite and foundry industries in Massachusetts.

Two principal causes led to the undertaking of this study in Massachusetts. In the granite industry, especially in the city of Quincy, the silicosis situation had a year ago become so acute that nearly all insurance companies had refused to write Workmen's Compensation policies, and coverage could be secured only from one company and at a rate based on the assumption that every worker then employed would become disabled or succumb to the disease within a period of ten years. Inclusion of the foundry industry in the investigation was due in the first place to the rapidly increasing number of claims for silicosis among foundry-workers in a number of States. In addition to this growing realization of the silicosis hazard in foundries, a dramatic incident occurred last April in a Massachusetts plant, where 42 workmen were summarily dropped because their employer was unable to secure compensation insurance after they had been declared to have silicosis on the basis of X-ray examination.

Under the provisions of a resolve of the General Court of Massachusetts, signed by the Governor on July 12, 1933, a special commission, consisting of the Commissioners of Labor and Industries, Public Health and Insurance, the Chairman of the Industrial Accident Board, and the Attorney General, was created to study the problem of diseases caused by dusts in the granite and foundry industries, the questions of prevention of these

[1] From the Massachusetts Department of Public Health. Data by courtesy of the special Industrial Disease Commission.

[2] Read at the annual meeting of the American Epidemiological Society, New York City, April 27, 1934.

diseases, and of compensation insurance in these industries. The medical phases of the investigation were assigned to the Department of Public Health.

METHOD OF EXAMINATION

Examinations of the workers were all made by members of the clinic staff of the Division of Tuberculosis in the Department of Public Health, men experienced in the diagnosis of pulmonary diseases. For convenience the medical history was taken in code by the examining physician. The principal items recorded were age, nationality, occupation (past and present) in the granite or foundry industry, and number of years in each occupation.

In addition to the medical history, a physical examination of the chest was made on each worker, including measurement of the chest on inspiration and expiration. Flat X-ray plates of the chest were taken for each worker by a technician of the State clinic with a portable apparatus set up in or near the plant. So far as physically possible a sputum specimen was obtained from each individual and examined in the State Laboratory. It should be remembered that the men examined were presumably well individuals and were either at work or temporarily unemployed at the time of the examination. Hence the examinations afford no measure of the number who may have been disabled as a result of their work.

To obtain a fair sample of workers in the granite industry of Massachusetts, examinations were conducted in plants in Quincy, Milford, Fitchburg and Westford. Of the 1,591 granite-workers in these towns 961, or 60.3 per cent, were examined. In the foundry industry 10 representative plants, located in 6 cities, were selected, where 1,614 employees were examined, or 75.4 per cent of all workers in these foundries. In both cases all workers were examined from whom consent could be secured, and, so far as could be determined, the samples obtained were representative of these two industries in the State.

CLASSIFICATION OF SILICOSIS

For the purposes of this study the American classification of Lanza and Childs has been adopted, and on the basis of X-ray examination the disease is divided into first, second, and third stages, in order of progression. Of these groups the first corresponds to the Canadian or South African "anteprimary" stage: the second, to the Canadian primary: and, the third, to the second stage of the Canadian classification. To

complete the picture it was found desirable to add two additional classifications: "suspect silicosis," which represents a degree of pulmonary fibrosis greater than normal, but not specifically diagnostic, and "silicosis and tuberculosis." It is recognized that any classification of silicosis into stages is arbitrary, but it is of some value, especially in the study of time relationships. Disability is not considered in this grouping, but only the degree of fibrosis as indicated by X-ray appearance. The Commission is deeply indebted to Dr. Leroy U. Gardner, Mr. Homer L. Sampson, and Dr. Henry K. Pancoast for their generous assistance in the interpretation of the X-ray plates, and the classification of cases found.

THE PROBLEM

The bases for the diagnosis of silicosis are too well established to call for discussion here. Suffice it to say that, utilizing the fundamental work of such men as Lanza, Childs, Russell, Mavragadato, and Gardner, it became a major problem of the Industrial Disease Commission to measure, so far as possible, the principal factors which determine the incidence of silicosis, tuberculosis, and other pulmonary diseases in granite- and foundry-workers in Massachusetts. Among these factors the following are generally accepted as fundamental in the production of silicosis:

1: The percentage of free silica in the inhaled dust
2: The concentration of silica particles less than 10 micra in diameter in the atmosphere
3: The duration of exposure to the dust
4: The susceptibility of the individual exposed, as modified by age, complicating infections, etc.

GRANITE INDUSTRY

Petrographic analyses by Professor E. S. Larsen, Jr., of Harvard University, showed a free silica content of approximately 20 per cent in samples of granite from Fitchburg and Westford, compared with 30 per cent of free silica in the Quincy and Milford granites. This represents a difference of 50 per cent in the proportion of free silica to which granite-workers in these two groups of towns are exposed, and constitutes a factor which must be considered in the development of silicosis.

Wide variations are found in the dust content of the air to which granite-workers are exposed in different occupations within the industry. Especially since the general adoption of automatic hand-tools this has

become so marked that for the purposes of this study the workers have been divided into three broad groups, based on the median dust counts found to prevail in their working environment. These groups, giving specific occupations and dust counts, are shown in table 1.

The dust samples were taken at the level of the operator's nose under as near average conditions of dustiness for the occupation as could be obtained. All samples were taken by the impinger method and by the

TABLE 1

Median dust counts in various occupations

OCCUPATION (1)	NUMBER OF MEN EXAMINED (2)	MEDIAN DUST COUNT IN MILLION PARTICLES PER CUBIC FOOT (3)	WEIGHTED AVERAGE OF MEDIAN DUST COUNTS FOR GROUP (4)
Group A:			
Lathe-operator	3	60.0	40.4
Pneumatic hand-tool operator	417	47.0	
Surface cutter	43	32.5	
Carver or letterer	45	25.6	
Group B:			
Sand-blaster	7	21.8	17.1
Other granite work	258	17.0	
Blacksmith	40	17.0	
Tool-grinder	3	17.0	
Group C:			
Sawyer	20	13.8	8.9
Quarryman	48	10.0	
Polisher	54	7.7	
Office	23	5.0	

same man, an engineer trained in dust determinations. Only particles of 10 micra or less were counted.

DURATION OF EXPOSURE TO DUST

Since the production of silicosis is a cumulative process, the length of time which the worker is exposed to silica dust becomes as important as the dust concentration to which he is subjected. In table 1 it was seen that the men exposed by their trade to the greatest dustiness were chiefly pneumatic hand-tool operators, surface cutters, and carvers. Table 2 shows that these employees, chiefly on account of the skill required in

their occupations, remain in the granite industry for substantially longer periods than the workers in groups B and C of table 1.

In the same way it was found that the length of service of granite-workers varied substantially in the different towns studied, Quincy and Milford both having a high proportion in the long-service group, while Fitchburg and Westford showed a preponderance of employees who had worked less than ten years in granite.

Figure 1 brings out rather strikingly the relationship of age of granite-workers to their length of service in the industry. From this it is evident that the majority of workers enter the trade early in life and that "once a granite-cutter always a granite-cutter" is the general rule. From this diagram it will be seen that, if the average number of years in industry

TABLE 2

Length of service of granite-workers in each dust-count group

DUST-COUNT GROUP (1)	LENGTH OF SERVICE (YEARS)						TOTAL (5)
	Under 5 (2)		5–9 (3)		10 and over (4)		
	Number	Per cent	Number	Per cent	Number	Per cent	Number
Group A	40	8	85	17	382	75	507
Group B	102	33	73	24	131	42	306
Group C	40	29	26	18	78	54	144
Totals	182		184		591		957

are known, the mean age can be determined roughly by the addition of 20 years.

THE INCIDENCE OF SILICOSIS

Since only one examination was possible in this survey all figures given concerning the incidence of silicosis necessarily represent purely a cross-section of the employee population actually working at the time of the examination.[3]

The association of the frequency of silicosis with length of service is emphasized in table 4, in comparison with table 3. The same relationship is also obvious in comparing the percentage of silicosis with the weighted average of length of service, while the mean incidence of silicosis by five-year periods is graphically shown in figure 2.

[3] In the following tables, cases of silicosis, both with and without tuberculosis, have been included.

As a measure of the two known factors, length of service and dust concentration, the specific incidence of silicosis, according to these

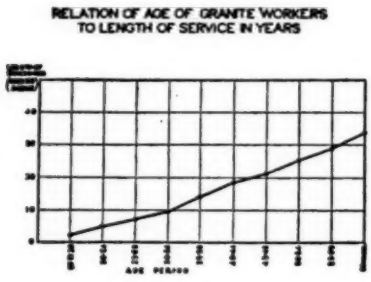

FIG. 1

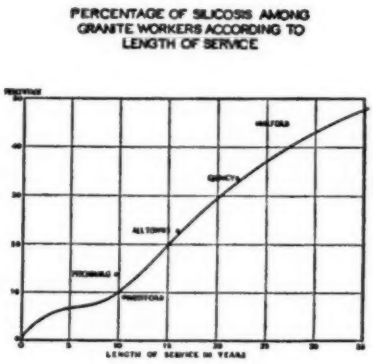

FIG. 2

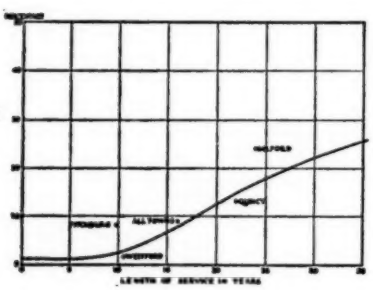

FIG. 3

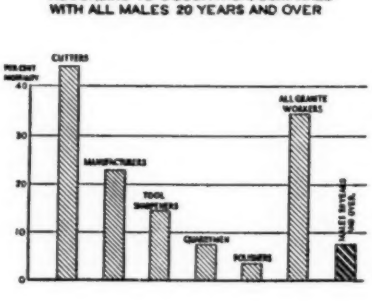

FIG. 4

FIGS. 1–4

TABLE 3

Distribution of granite-workers according to length of service and residence

RESIDENCE (1)	UNDER 10 YEARS (2)		10–24 YEARS (3)		25 YEARS AND OVER (4)		TOTAL (5)	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Quincy	60	15.0	187	47.0	151	38.0	398	100.0
Milford	16	18.4	29	33.3	42	48.3	87	100.0
Fitchburg	52	59.0	18	20.5	18	20.5	88	100.0
Westford	239	62.2	104	27.2	41	10.6	384	100.0
Totals	367		338		252		957	

variables, has been computed in table 5. Here it will be noted that after the first ten years of exposure the incidence of silicosis varies directly with both dustiness of environment and length of service.

TABLE 4

Percentage of silicosis by towns

TOWN (1)	NUMBER EXAMINED (2)	NUMBER WITH SILICOSIS (3)	PER CENT WITH SILICOSIS (4)	WEIGHTED AVERAGE OF LENGTH OF SERVICE IN YEARS (5)
Westford	387	34	8.9	10.6
Fitchburg	88	12	13.6	9.7
Quincy	399	134	33.6	22.0
Milford	87	39	44.9	24.0
Totals	961	219	22.8	16.0

TABLE 5

Silicosis in dust-count groups according to length of service

Cases of silicosis

DUST-COUNT GROUP (1)	LENGTH OF SERVICE IN YEARS						TOTAL (5)	
	Under 10 (2)		10–24 (3)		25 and over (4)			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Group A	6	4.8	67	31.9	108	62.8	181	35.7
Group B	8	4.6	9	10.8	10	20.8	27	8.8
Group C	4	6.0	5	11.1	2	6.3	11	7.6
Totals	18	4.9	81	23.9	120	47.6	219	22.8

TABLE 6

Stage of silicosis according to length of service

CLASSIFICATION (1)	LENGTH OF SERVICE IN YEARS						TOTAL (5)	
	Under 10 (2)		10–24 (3)		25 and over (4)			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Negative for silicosis	320	87.2	196	58.0	97	38.5	613	64.1
Suspect silicosis	29	7.9	61	18.0	35	13.9	125	13.1
Silicosis, stage 1	17	4.6	66	19.5	57	22.6	140	14.6
Silicosis, stage 2	1	0.3	15	4.4	57	22.6	73	7.6
Silicosis, stage 3	0				6	2.4	6	0.6
Totals	367	100.0	338	100.0	252	100.0	957	100.0

The importance of the time element in the production of silicosis is brought out even more specifically in table 6. Not only does the incidence of silicosis increase with length of service, but long periods of exposure to siliceous dust appear to be essential to the development of advanced stages of the disease.

HISTORY AND PHYSICAL SIGNS

Of the 961 granite-workers examined, only 6.0 per cent gave any history of known exposure to tuberculosis, and only 11.7 per cent had any complaints. In order of frequency, these complaints were cough, dyspnoea, loss of weight, and fatigue. The incidence of complaints was highest in the group with tuberculosis and silicosis, and next in those with silicosis alone. Dulness and râles were found in only 8 per cent of the whole group. Even among the workers with silicosis and tuberculosis râles were elicited in only 23 per cent.

Limitation of chest expansion was found to be primarily a function of advancing age rather than of pulmonary fibrosis. Only in cases with tuberculosis in addition to silicosis was there a possibly significant relationship between chest expansion and pulmonary disease.

SILICOSIS AND TUBERCULOSIS

The high incidence of tuberculosis relatively late in life among workers exposed to certain types of dust has been recognized for at least a hundred years (1). This predisposing effect of dusts on phthisis was until recently believed to be due to the mechanical irritation of the inhaled particles, but the careful experimental work of Gardner (2) and others has shown that free silica is the essential aetiological agent involved, apparently through solution in the body fluids. That the action of silica in favoring the development of tuberculosis is chemical or physiochemical rather than mechanical is substantiated by the observation that the addition of free silica to culture media definitely stimulates the growth of tubercle bacilli.

Among granite-cutters tuberculosis is of peculiar importance, because it is in the great majority of cases the terminal factor in silicosis. In the individual the association of silicosis and tuberculosis may be so intimate that in the advanced stages it is almost impossible to distinguish one from the other, or to determine the order of precedence. In most cases the distribution and roentgenological appearance of the lesions make it possible to distinguish the complicating infection. In this series it was possible to obtain only a single specimen of sputum from each worker,

and that of course only from individuals who were expectorating. In this way positive sputa were obtained from 4 granite-workers, or 5.5 per cent of those who showed pulmonary infiltrations characteristic of tuberculosis.

Comparison of figure 3 with figure 2 indicates that among granite-workers tuberculosis develops even more slowly than silicosis. It is distinctly a disease of late industrial life, developing chiefly on a soil previously prepared by pulmonary fibrosis, and apparently influenced by the same factors which have been found to play such an important part in the development of silicosis, namely environmental dust concentration, and length of service. To these factors must be added, of course, exposure to tuberculous infection. In table 7 there is at least a sugges-

TABLE 7

Tuberculosis in dust-count groups according to length of service*

DUST-COUNT GROUP (1)	LENGTH OF SERVICE IN YEARS						TOTAL (5)	
	Under 10 (2)		10–24 (3)		25 and over (4)			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Group A			24	11.4	52	30.2	76	15.0
Group B	2	1.5	3	3.6	3	6.7	8	2.6
Group C	1	1.5			1	3.1	2	1.4
Totals	3	8.2	27	8.0	56	22.2	86	9.1

* This group consists of 73 cases of tuberculosis and silicosis, 9 of tuberculosis only, and 4 of tuberculosis with suspected silicosis.

tion that both high dust concentration and long exposure are essential to the frequent development of tuberculosis.

TUBERCULOSIS IN GRANITE-WORKERS

To throw further light on the importance of tuberculosis as a disease of granite-workers, transcripts were made of the death-certificates for all deaths among such workers in Quincy and Milford for the years 1921–1932, inclusive. Resident deaths occurring elsewhere were reallocated to these towns. Because it was not possible to obtain the actual number of granite-workers living in these communities specific death-rates could not be computed, but the proportionate mortality from tuberculosis among such workers, as compared with all males of 20 years and over in Massachusetts, is given in figure 4. While it is recognized that propor-

tionate mortality is subject to various errors a ratio of the order of 5 or 6 to 1 is obviously significant.

In Quincy and Milford the Granite Cutters International Association fortunately had records of the membership of the Union, and of the number of deaths of cutters, by years. Through the coöperation of the Union officials these records were made available and the records of deaths were checked against the original death certificates. In this way specific death-rates among granite-cutters were obtained for a period of twelve years. Here again in table 8 we have ample confirmation of the tremendous toll of tuberculosis among granite workers.

TABLE 8

Tuberculosis mortality rates per 100,000 for Quincy and Milford Union cutters only, by years 1921–1932

YEAR (1)	COMBINED UNION MEMBERSHIP (2)	NUMBER DEATHS FROM TUBERCULOSIS (3)	TUBERCULOSIS DEATH-RATES PER 100,000 CUTTERS (4)	TUBERCULOSIS DEATH-RATES PER 100,000 MALES 20 YEARS AND OVER (5)
1921	920	10	1,087	141
1922	774	14	1,809	145
1923	833	9	1,080	133
1924	824	6	728	133
1925	796	11	1,382	125
1926	768	6	781	133
1927	822	11	1,338	120
1928	790	6	759	114
1929	773	8	1,035	108
1930	778	6	771	106
1931	722	13	1,801	99
1932	715	9	1,259	88
Totals.....	9,515	109	1,146	112

Further inferential evidence of the influence of occupation on tuberculosis in granite-workers is furnished by the age distribution of tuberculosis deaths in that group. For all males in Massachusetts the peak of proportionate tuberculosis mortality is reached in the age group 20–29. Among granite workers the accompanying diagram shows that the tuberculosis mortality continues to rise for an additional twenty years, and remains about four times as high for the rest of life.

FOUNDRY INDUSTRY

While the foundrymen have been divided into three groups, similar to those given for granite-workers, according to the dustiness of their work-

ing environment, certain differences should be noted. For the granite industry the dust counts for each group averaged somewhat higher than the corresponding group in foundries. In the granite sheds it was seen that the cutters, who remain longest in the industry, are by the nature of their work exposed to the greatest dustiness. In the foundries the skilled, long-service group consists of the moulders who are exposed only

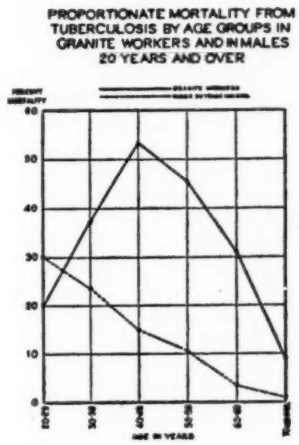

FIG. 5

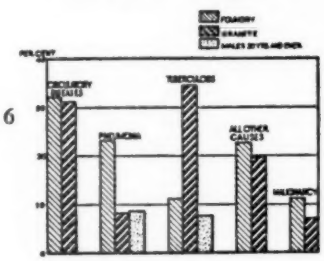

FIG. 6

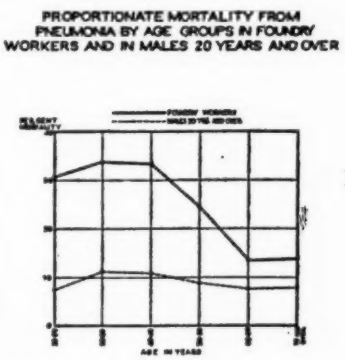

FIG. 7

FIGS. 5–7

to the general dustiness of the moulding floor, while the highest dust concentrations are found in the shake-out and casting cleaning departments. The silica content of the foundry dusts analyzed varied widely, but for particles of 10 micra or less averaged somewhat lower than that of the granite dusts.

Of the 1,641 foundrymen examined, 8.8 per cent were found to have uncomplicated silicosis and 2.6 per cent silicosis and tuberculosis, a total of 11.4, compared with 22.8 per cent in the granite-workers. In only one

TABLE 9

Median dust counts in various occupations

OCCUPATION (1)	NUMBER OF MEN EXAMINED (2)	MEDIAN DUST COUNT IN MILLION PARTICLES PER CUBIC FOOT (3)	WEIGHTED AVERAGE OF MEDIAN DUST COUNT FOR GROUP (4)
Group A:			
Sand-chipper	15	266	
Sand-preparation	8	63	
Sand-blaster	30	35	
Grinder	53	31	32
Shake-out	71	19	
Cleaning room	71	10	
Chipper	69	6	
Group B:			
Moulding floor	565	14	
Craneman	48	14	14
Melter	60	11	
Group C:			
Core-room	113	1	5
Other foundry	511	6	

TABLE 10

Silicosis by dust-count groups according to length of service

DUST-COUNT GROUP (1)	LENGTH OF SERVICE IN YEARS						TOTAL (5)	
	Under 10 (2)		10–24 (3)		25 and over (4)			
	Foundry	Granite	Foundry	Granite	Foundry	Granite	Foundry	Granite
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Group A	5.1	4.8	20.6	31.9	43.7	62.8	14.0	35.7
Group B	4.6	4.6	12.1	10.8	34.3	20.8	16.1	8.8
Group C	0.7	6.0	5.6	11.1	25.9	6.3	5.3	7.6
Totals	3.3	4.9	11.1	23.9	32.6	47.6	11.5	22.9

TABLE 11

Tuberculosis by dust-count groups according to length of service

DUST-COUNT GROUP (1)	LENGTH OF SERVICE IN YEARS						TOTAL (5)	
	Under 10 (2)		10–24 (3)		25 and over (4)			
	Foundry	Granite	Foundry	Granite	Foundry	Granite	Foundry	Granite
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Group A	2.3	0	10.3	11.4	12.5	30.2	6.0	15.0
Group B	2.0	1.5	2.0	3.6	8.7	6.7	3.7	2.6
Group C	1.1	1.5	1.4		8.5	3.1	1.9	1.4
Totals	1.7	0.8	3.2	8.0	8.9	22.2	3.5	9.1

of the 10 plants was no silicosis or silicosis with tuberculosis found. When all foundry-workers were grouped according to occupation it was found that each occupation yielded a certain proportion of silicosis.

Although the proportion of tuberculosis in the foundrymen examined was only about one-third that found in granite-workers it is seen to vary in the same way with the dustiness of the environment and the duration of exposure.

Computation of the proportionate mortality from the principal causes of death among foundrymen gave some surprising results. From tuberculosis, the mortality is about 50 per cent higher than that among males of 20 and over, but from pneumonia it is three times that in either granite-workers or in the general population.

When the proportionate mortality from pneumonia is arranged by age groups (figure 7), it is apparent that the excess among foundry-workers extends from age twenty through the rest of life, though it is greatest below the age of sixty; that is, it corresponds in general with the active working-age of the foundryman.

The excess mortality from pneumonia in iron- and steel-manufacturing towns has several times been pointed out. In an excellent study by the United States Public Health Service (3), it was found that the highest incidence of pneumonia was among the workmen exposed to the greatest heat and to extreme changes of temperature. From our data it has not been possible to go further into the specific causes of this excess pneumonia mortality, but it is indicated as the greatest occupational hazard in the foundry industry in Massachusetts.

COMMENT

It is hardly possible to leave the silicosis problem at this time without some mention of sericite, the hydrated silicate of aluminum and potassium, recently mentioned as the causative factor in silicosis (4). In this connection it may be said that petrographic analysis showed sericite in significant amounts in the granite of only one city studied, Fitchburg, where the incidence of silicosis was low. In the granite from Milford, where silicosis was more than three times as frequent, barely a trace of sericite was found.

CONCLUSIONS

1. In representative groups of both granite- and foundry-workers in Massachusetts the frequency of silicosis, and of silicosis with tuberculosis,

was found to be positively correlated with the duration of exposure to dusts containing free silica and to the concentration of such dusts in the occupational environment.

2. Among the granite workers examined silicosis alone was found in 15.2 per cent, and silicosis complicated with tuberculosis in 7.6 per cent.

3. Tuberculosis is the cause of death in over one-third of all granite-workers, a proportionate mortality three times that in foundry-workers, and four times that in all males of 20 years and over.

4. Among the employees of 10 Massachusetts foundries, silicosis was found in 8.8 per cent and silicosis with tuberculosis in 2.6 per cent, a total frequency of one-half that found in granite-workers.

5. The silicosis found in foundrymen was not only less frequent but also less advanced in degree than that in granite-workers.

6. Though there is an excess of tuberculosis deaths among foundry-workers, pneumonia, which is the cause of about one-fourth of all deaths of foundrymen, appears to be the greatest occupational hazard in the industry.

REFERENCES

(1) ALLISON: Trans. Med. & Chir. Soc., Edinburgh, 1824, i, 373.
(2) GARDNER, L. U.: Jour. Industr. Hyg., 1932, xiv, 18.
(3) Public Health Bulletin, 1932, no. 202.
(4) JONES, W. R.: Jour. Hyg., London, 1933, xxxiii, 3.

THE TISSUE REACTIONS OF THE LUNG TO THE INTRATRACHEAL INJECTION OF PARTICULATE SERICITE[1]

An Experimental Study

WILLIS S. LEMON[2] AND GEORGE M. HIGGINS[3]

We have reported previously the reactions that take place in the lungs of experimental animals following the intratracheal injection of particulate mineral substances (11, 12) and of *Mycobacterium tuberculosis* (10). It was possible to demonstrate the similarities of the reactions (6) and the pulmonary lesions resulting from the introduction of pure uncombined silicon-dioxide and *Mycobacterium tuberculosis*, and to distinguish the differences between the pathological changes brought about by quartz particles and those of aluminum-oxide and of borosilicate-glass.

In this report we shall describe the reactions and the lesions produced when the mineral substance, *sericite*, is introduced into the lungs under similar conditions, using the same species of animal and using the same technique of preparation and method of introduction. It is hoped that the study may serve to introduce evidence of some value in determining the significance of sericite as an aetiological factor in the production of silicosis.

Review of the Literature

At the International Conference, Johannesburg, August, 1930, a report was given by Gardner, Middleton, and Orenstein on the medical aspects of silicosis, including aetiology, pathology, and diagnosis. They defined silicosis as a pathological condition of the lungs due to inhalation of silicon-dioxide, in a chemically uncombined condition, which reached the lungs either alone or as a mixture with other dusts; and stipulated that the silica must be in the form of particles of the order of less than 10 micra. Additional aetiological stipulations specified that exposure must be to an atmosphere of sufficient concentration and amount of dust and throughout a certain period of time. The authors

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expressed the opinion that silica dust played the dominant rôle in the production of silicosis, though they agreed that the admixture of other dusts tended to modify the pathological changes in the lungs so that these resembled those of other forms of pneumonoconiosis, and that the modification bore some relation to the percentage of free silica in the mixture. They recognized that the inhalation of silicates in the form of asbestos produced a definite pneumonoconiosis, and that other dusts, such as those from marble, coal, carborundum, and so forth, produced demonstrable changes in the lung. These changes were represented by a fibrosis, brought about because relatively insoluble, minute particles of minerals in sufficient concentration had been brought by the activity of phagocytic cells into intimate contact with the pulmonary connective tissue.

Simson (17) described that form of fibrosis which results from the prolonged and continuous inhalation of harmful dusts other than silica. His description was based on the fibrosis resulting from the inhalation of asbestos; it is equally satisfactory, however, for other dusts that are relatively inert, insoluble, and in particles of sufficient concentration and size permitting phagocytosis by phagocytic alveolar cells. The fibrosis produced is a diffuse cellular one that occurs in the walls of the bronchioles and all of their finer divisions. It extends so as to involve the supporting connective tissue of the adjacent blood-vessels, and to some extent also the walls of adjacent alveoli:

> In very advanced cases of the condition, the fibrosis may extend to the septa, to the supporting tissues of the bronchi and larger blood vessels, and to the alveolar walls. Even in these cases, the greatest degree of fibrosis is localized to the supporting tissue about the entrance to the primary unit. It may advance to such a degree that the bronchioles become constricted, sometimes retaining their circular outline in cross section, sometimes being reduced to mere slit-like openings. Rounded nodules of cellular character are sometimes seen, but the dense hyaline type of nodule is usually absent. Dust containing only a small percentage of silica may also give rise to these changes, and there is a greater liability to generalized fibrosis when a low-grade type of infection (not necessarily of tuberculous origin) complicates the dust effect. . . . The changes just described appear to be the primary lesions caused by the inhalation of any injurious dust, but when the great majority of the inhaled particles are composed of or contain silica, there develops, in addition, a specific and localized type of fibrosis,—the silicotic islet.

In this description by Simson there is nothing to suggest a resemblance to the orderly whorled arrangement of cells and fibres and the sharp definition from the adjacent parenchyma of the silicotic nodule. It is quite similar to the description given by Badham (1) and Simson (18) of the pneumonoconiosis observed at Broken Hill and of the fibrosis of the lung due to hematite dust described by Cronin (4) and Goadby (8). The descriptioni s not unlike that of Bohrod (3) in his observations on pulmonary siderosis.

Typical silicotic lesions may be produced experimentally by various methods if silica in suitable amount and size of particles is introduced into the lungs of

animals. We (11) (12) were unable to produce lesions even remotely like them when either aluminum-oxide or borosilicate-glass was similarly introduced. These substances produced lesions similar to those developed after inhalation of any harmful mineral in particulate form. We were of the opinion that silicosis resulted from the reaction of the tissues of the lung to uncombined silicon dioxide.

The unanimous opinion of workers and investigators in Australia, South Africa, Germany, England, Canada, and the United States is that "silicosis is a pathological disease of the lungs due to inhalation of silicon dioxide" and "that it can be produced experimentally in animals." It is conceded that many dusts may create a generalized fibrosis, but only one, namely, uncombined silicon-dioxide, produces the special form of fibrosis characteristic of silicosis.

The only challenge to the opinion regarding the aetiology of silicosis expressed in the report accepted by the International Conference is found in an article by William R. Jones (9). Jones was investigating, in the South Wales coal-field, cases of silicosis that developed among miners who were working in the collieries of the anthracite district. His object was to prove whether or not their work brought them into contact with dust from rocks which came under the category of "silica rock" as defined in English law, for the purpose of determining compensation under the *Silicosis Schemes*. He found cases of silicosis but was unable to find rock in the mines that contained sufficient silica to permit being included in the Schemes. He found, however, that the rocks contained silicates in the form of sericite. On examining the lungs of miners who had died of silicosis, he found that such lungs also contained silicates rather than silica. He then examined the rocks in the Scottish coal fields where silicosis had never been reported. The sandstones examined by him fulfilled the legal definition of silica rock, but did not contain sericite. He then studied and contrasted the mineral content of rock from the Kolar goldfield in India and of rock from the gold-bearing quartz conglomerate (Banket) of the Transvaal in South Africa. In India he could find no record of reported cases of silicosis. In South Africa he found such a high incidence of silicosis that the cost of the care of the miners affected by miner's phthisis amounted to a million pounds annually. The rock at the Kolar fields contained 90 per cent pure silicon-dioxide, chemically uncombined, but containing no sericite. The rock at the South African mines contained from 80 to 90 per cent uncombined silicon-dioxide, but it also contained a large percentage of sericite. By analysis Jones found the amount of sericite ranked next to that of silicon-dioxide in these rocks.

Jones's third investigation showed that the Broken Hill mines in New South Wales contained rock which had only a very small percentage of uncombined silicon-dioxide. George reported only 14 per cent of silica, which represents too small a concentration of silica in the dust to cause true silicosis and too

small a percentage to fulfill the definition of silica rock required for compensation in English law. Jones found that sericite was abundant in the rock at Broken Hill, along with sillimanite or fibrolite, which is an aluminum-silicate and is similar in form and chemical composition to sericite. Sericite is known as white mica and is a hydrated silicate of aluminum and potassium. Sayers (15), in 1925, and Badham (2) and George (7), in 1930, also had discussed the relationship of the peculiar type of pneumonoconiosis found at Broken Hill and the low content of free silica in the ore worked by the miners. Badham stated that "he was in no way convinced that the disease which they found in Broken Hill was the pure type of silicosis found in Johannesburg." He further said that many of these men had worked in dust containing proportions of silica ranging up to 35 per cent, and from observations he was by no means convinced that the silica was the whole story of their disease. He found confirmation of that view in the fact that where they had, as in Broken Hill, 85 per cent of silicates, most of them intractable, they found in the lung after death intractable and other silicates. It was reasonable for Badham to assume that silicates had a considerable effect on the production of fibrous pneumonoconiosis.

Jones not only showed that rock might contain a high percentage of silica and still not produce silicosis in the men working in the mines, but he also showed that there was a high incidence of silicosis wherever miners encountered rock rich in the silicate, sericite. He showed that this mineral was contained in the lungs of those miners who had died of silicosis, proving its presence by examination of histological sections with the polarizing microscope and by chemical analysis of the ash obtained from the lungs. He believed that the bulk of the finest mineral particles in a silicotic lung consisted of minute fibres of silicate minerals, chiefly of sericite. His conclusions regarding the aetiology of silicosis, based on the result of these investigations, were opposed to those accepted at the International Conference. He epitomized his view by concluding,

> Silica in the uncombined state, as quartz, is not the chief cause of silicosis in these and certain other cases. This appears to be conclusively established, it is submitted here, by the following facts: . . . (a) the amount of quartz and the size and form of the quartz grains in the sandstones occurring in the underground working places in the Scottish coalfields and the South Wales coalfield are alike. The latter sandstones give rise to dust that has caused scores of cases of silicosis, whereas no authorized case of silicosis has been produced in the Scottish coalfields. (b) The gold-bearing quartz conglomerate of South Africa gives rise to dust that has caused thousands of cases of silicosis; the gold-bearing quartz rock of the Kolar Goldfield, India, contains more quartz than the South African rock and yet produces dust that has caused no case of that disease. (c) No quartz-bearing rocks investigated by the author are known to have given rise to silicosis-producing dust except those which also contain abundance of fibrous aggregates of sericite or of fibrous silicate minerals, loosely held together and easily freed into the atmosphere when the rock is drilled and blasted. (d) Rocks which contain a relatively small percentage of quartz (well below the minimum amount in the rock types named in the Silicosis Schemes under English law) but which do contain fibrous silicate

minerals such as sericite and sillimanite, as for example, at Broken Hill Mines, New South Wales, produce dust that has caused a large number of silicosis cases.

METHODS OF EXPERIMENTATION

Two different samples of sericite were obtained through the courtesy of Mr. H. G. Clinton, geologist, of Manhattan, Nevada, and of Dr. Leroy U. Gardner (5), of Saranac Lake, New York, who had obtained the material from Pickens County, Georgia, and had had it petrographically examined and found to be free of uncombined silica. Two separate series of rabbits were given intratracheal injections of these materials by the same technique as was used in our reported experiments in which we injected aluminum-oxide and borosilicate-glass. The sericite was prepared by Osterberg (13) and was ground to the same degree of fineness as the other mineral substances we have used, so that the powders consisted of extremely small particles, the majority of which were less than 5 micra in diameter. A large percentage were so fine that they exhibited brownian movement when examined microscopically. The same amount of sericite by weight was suspended in 3 cc. of normal saline solution and given in one dose. All procedures were carried out under aseptic technique and all animals were anaesthetized by amytal injected intravenously. In each series the animals were killed by over-etherization at regularly spaced intervals during a total period of twenty weeks.

RESULTS

The reactions to the two samples were so nearly identical that no effort will be made to describe the lesions separately. Attention will be called only to those rare differences which were observed, especially with reference to the effect of the mineral substances on the phagocytic cells that composed the lesion.

In the experiment of one week's duration, the lungs on gross examination showed no evidence of nodular lesions. The lungs were hyperaemic but not consolidated, the pleura was smooth and the subpleural tissue free from visible or palpable miliary lesions. On section, the lungs, especially the lower lobes, were found to be hyperaemic and partially consolidated. On microscopical examination, areas of bronchopneumonia were encountered along the course of the bronchi. These were largest at the hilum and decreased in size toward the periphery of the lung. The size of the consolidated lesions had a very definite relationship to the size of the bronchus or vessel to which they were related.

Sometimes the lesions were eccentrically placed, sometimes they completely surrounded and sometimes they seemed to form a cellular sheath for these structures, the apearance in all probability depending upon the angle of sectioning. It appeared that the partially consolidated portions of lung resulted from atelectasis, due to the administration of 3 cc. of fluid suspension, combined with inflammation produced by the suspended mineral substance. All the agencies employed in the eradication of the foreign substance showed remarkable evidences of activity. The alveolar phagocytes were in all stages of desquamation, while some were partially and some were completely detached from the alveolar walls. Large numbers of these phagocytic cells were packed together at the termination of the alveolar ducts and their subdivisions and in the subpleural tissue. Exudates, made up of cells derived from the blood and also of phagocytic cells, were seen in all the bronchial lumina, and phagocytic cells could be demonstrated in the lymph-vessels, in the bronchial lymph follicles, and in the lymph nodes at the hilum. On examination with the polarizing microscope, intracellular sericite could be seen whereever hyperplastic tissue occurred, as well as in the bronchial exudate and in the lymph nodes at the bifurcation of the trachea.

During the first week succeeding intratracheal injection, sericite was being phagocytosed and eliminated by way of the lymphatics and the air-passages. That which remained in the lung was being stored in peribronchial, perivascular and subpleural tissues. In these regions the phagocytic cells showed early evidence of degeneration and disintegration. They had lost their staining character, they were pale, and vacuolated and abnormally shaped because their limiting cell-membranes had become indistinct or had disappeared.

When two weeks had passed, the lungs of the animals had lost all evidence of congestion and of the partial consolidation that could be interpreted as due to atelectasis. Very tiny, impalpable and indistinct lesions could be seen on the surface of the pleura. These were somewhat paler than the normal pleura. On section, grayish miliary lesions could be seen and could also be palpated. They were visible mainly at the hilum, but very small similar lesions could, with care, be visualized along the course of the bronchi. Microscopically, lesions could be seen that were too small to be identified on gross inspection or on palpation. These small lesions were made up of irregularly-shaped groups of cells lying in the perivascular, peribronchial, and subpleural tissues, and especially at the terminations of the alveolar ducts and along the walls

of the stria. In the parenchyma surrounding the cellular islets, the alveolar walls themselves were thickened by large numbers of mononuclear phagocytic cells.

The sericite from Nevada seemed to be more toxic for the mononuclear phagocytic cells than that sent us by Dr. Gardner. The Nevada sericite caused a very marked degeneration of the phagocytic cells, so that the lesion had a homogeneous appearance without distinguishing outlines of cells. Nuclei alone remained to identify the cellular nature of the lesion, although here and there the outline of a cell could be observed if its degeneration was less complete than the others making up the cellular islet. The appearance resembled that of amyloid degeneration, but amyloid was not found when specific staining methods were used. The islet cells undergo fatty degeneration, but the homogeneous degeneration we have observed was not produced by intracellular fat. By polarized light, intracellular particles were found in all regions where lesions existed, either as irregular or ill-defined islets, or as cellular inclusions in the alveolar and bronchiolar walls. In those collections commonly found about the terminals of the alveolar duct, large numbers of particles were always seen. They could be identified in the lymph follicles of the larger bronchi but were never seen within the mucosa of the bronchi. We have never seen phagocytic cells in transit from the peribronchial tissue to the lumen of a bronchus. In the bronchial exudates mineral particles were found included within the protoplasm of the phagocytic cells. Inasmuch as a cellular exudate was seen in all orders of bronchioles and bronchi and never within their mucosa, it appears that the cells composing the exudate had been carried along within the bronchial lumina and had not reached them by penetration of their walls. In certain regions, the subpleural lesions included all tissue bordering on the pleura and these were limited only by the pleural endothelium. Such groups of cells were often found at the point of origin of the pulmonary vein. Myriads of particles could be seen within the protoplasm of the cells composing such lesions. In one section, by chance, an interlobular vein was cut longitudinally. Throughout its length lesions were found in the perivascular tissue, and an islet was observed at the source of the vein in the pleura. These lesions resulted from the "pleural drift" of cells from the parenchyma by way of the lymphatic structures that accompany the interlobular vein. When sections were specially stained to show fibrous tissue, it was apparent that fibrosis had already begun. This was repre-

sented by a fine network of fibres in the walls of all the finer bronchiolar divisions. The fibres of the network intermingled with those of the connective tissue of adjacent blood-vessels and bronchi. There was not the slightest evidence of the orderly whorled arrangement of fibres that we have observed in the silicotic islets of equal age.

In the following six weeks, the changes consisted mainly of a decrease in the size of the lesions, in a lessening in their numbers, and in an increasing degree of fibrosis. When the lesions (figure 1) were of this age-group, they showed very marked evidence of cellular disintegration and a conspicuous absence of a fibrous envelope that might serve as a sharp boundary-line between the islet and the enveloping parenchyma. At the periphery of these ill-defined and irregular groupings of degenerating or dead cells, there were large numbers of phagocytic cells showing variable but minor degrees of disintegration. The cells had distinct outlines and were vacuolated and well-stained. They were alveolar phagocytes;

Fig. 1. Peribronchial collection of phagocytic cells, showing their degeneration and death. Living phagocytes will be seen lying free in the alveolar spaces (8 weeks).

Fig. 2. Sericite in pulmonary tissue and in bronchial exudate (4 weeks)

Fig. 3. Coarse disseminated fibrosis (4 months)

Fig. 4. Fine diffuse fibrosis (3 months)

Fig. 5. Phagocytic cells in the lumen of a small bronchus (12 weeks)

Fig. 6. Cellular débris in the lumen of a peribronchial lymph vessel (12 weeks)

sometimes they were in their normal relationship to the alveolar wall, sometimes they were partially detached from it, more often they were completely detached and lying free in the alveolus. By examination under polarized light (figure 2), these cells could be seen to contain sericite. The lymphatics contained similar cells and the bronchi had similar cells as part of their exudates. In the animals which had lived for six and eight weeks, new lesions were observed that were similar to those formed in experiments of one- or two-weeks duration. These facts seem to be acceptable evidence that the cells in the originally formed lesions degenerate and die, and set free the sericite which they contain in their cytoplasm. The alveolar phagocytes at the periphery of the islets engulf the free sericite; the process of lymphatic and bronchial exclusion is started again and new lesions are created by the packing together of residual cells. There is no evidence that the phagocytic cells increase in numbers or that they are changed into fibroblasts and take part in the diffuse fibrosis that develops within two months.

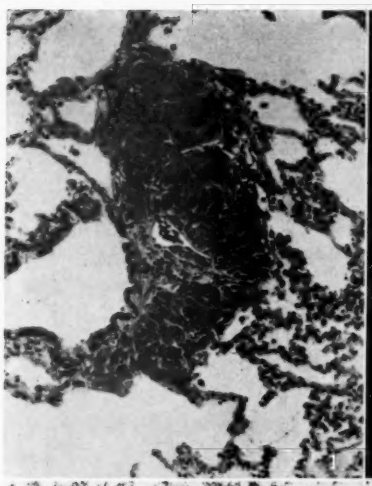

FIG. 1

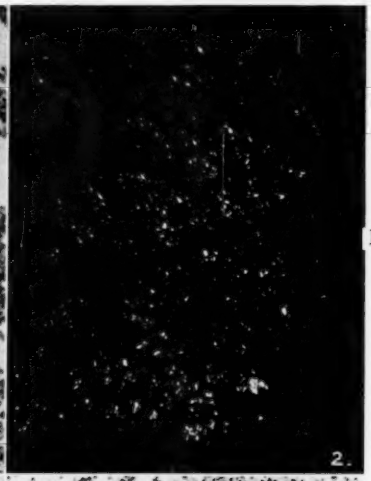

FIG. 2

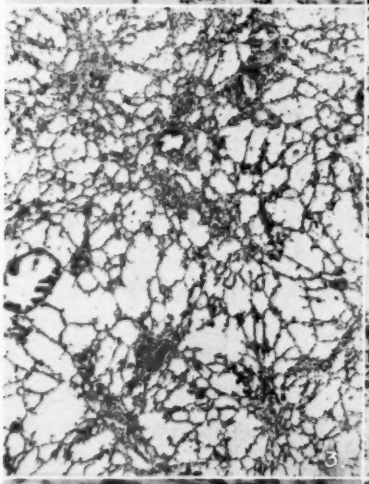

FIG. 3

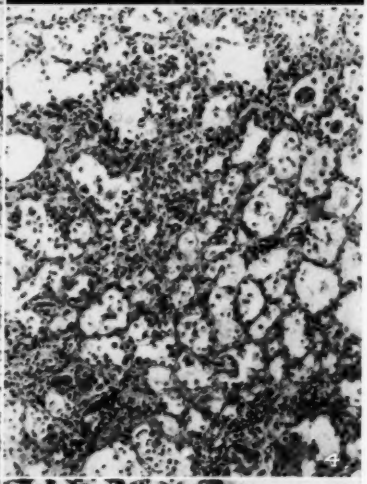

FIG. 4

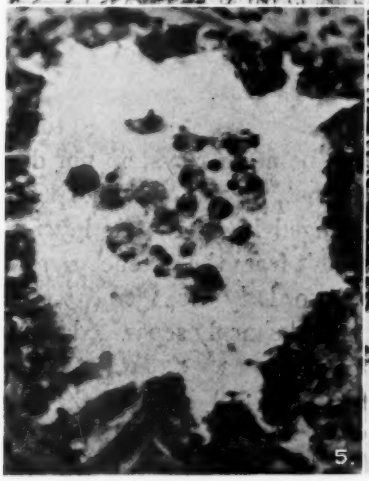

FIG. 5

FIG. 6

FIGS. 1–6

In experiments of three- to five-months duration, very small lesions could be seen and palpated if great care were taken in the examination. Care was necessary because of the small size of the lesions, their indistinct boundaries, their absence of nodular form, and their similarity in consistency to normal tissue. In contrast, we had found that silicotic nodules revealed themselves at first glance and touch because they were distinctly colored, definitely nodular, sharply separated from normal tissue, and distinctly denser and harder than the parenchyma into which they were set down as sharply defined islets.

Microscopically, it was apparent that there were larger numbers of lesions than could be observed on gross examination. The lesions were distributed throughout the lungs in the same locations as already described. The lesions that escaped identification at gross examination were minute and discretely placed in the peripheral portions of the parenchyma. The larger confluent lesions were placed eccentrically to larger bronchi and vessels, or formed a collar about them. Mechanisms of elimination already described, and degeneration of the cell aggregates, were the conspicuous processes. The evidence of fibrosis, though not entirely wanting, was yet of minor importance. Fibrosis (figure 3) was chiefly confined to the ramification of fibres centered about terminals of the finest bronchiolar subdivisions and passing out like spider-webs into the adjacent parenchyma. The alveolar walls were thickened and straightened so that distortion was created, and the parenchyma appeared altered and broken up into squares, circles, and oblongs. The smallest bronchioles were compressed, the walls of the vessels were thickened, and their calibre was reduced. In the larger confluent lesions (figure 4) the architecture of the lung was quite lost in a mass of diffuse fibrosis. By special staining methods reticulin was markedly increased in amount, and appeared in heavy strands which interlaced and ramified to create a felt-like appearance. There seemed to be neither system nor design in the arrangement of the fibres. In contrast, we observed in experimental tuberculosis that the fibrils were arranged in concentric layers which encapsulated the tubercle and separated it from the parenchyma. Similarly, in experimental silicosis the same orderly arrangement tended to encapsulate the silicotic islet or nodule and sharply separated it from the normal parenchyma.

In all experiments of more than four months' duration there was no evidence of gross pathological changes. The microscopic examination, however, showed the presence of small lesions, but their distribution and

general appearance were not different from that already described. Degenerated lesions, small fresh aggregations of cells, and phagocytic cells lying in alveolar spaces and as exudates in the bronchioles and bronchi (figure 5) or within lymph-channels (figure 6) were seen constantly. Reticulin was found as ramifying fibrils passing outward into adjacent tissue from the focal point where the lesion was located. Particles of sericite could be seen by examination with the polarizing microscope wherever hyperplasia occurred and wherever there were groups of degenerating phagocytes. The myriads of particles seen in younger lesions were no longer discovered; rather, the particles were few in number and much reduced in size. There also were many extremely fine points of light which seemed to represent the smallest particles that had either been introduced as such or had been reduced in size by the solvent action of tissue juices. Some were so very small they suggested that there might be many more minute enough so that they could no longer refract light and make themselves visible.

COMMENT

We realize that our results may not exactly represent the pathological changes produced by the inhalation of sericite by miners. The lesions were created in a brief time, and after the intratracheal injection of a single large dose of minute particles of the mineral substance suspended in saline solution, rather than by a continuous inhalation of the dry dust over long periods of time. There are also nonspecific effects from the bulk of the foreign body and the fluid injected, so that the earliest reactions include pulmonary atelectasis and partial consolidation. Gardner has quite justly criticized the method employed because of these faults. However, we have continued its use because of its comparative value in studying the reactions when different substances are used and because the lesions are developed within a relatively short time. Moreover, we have found that the lesions themselves are remarkably similar to those produced by the experimental inhalation of the same dust, or by inhalation by workers exposed to the dust incidental to their work in the dusty trades. The silicotic lesions we produced, either as single islets or as conglomerate lesions, can hardly be distinguished from those illustrated by Policard (14), or by Simson, Strachan and Irvine (19), or by many other workers throughout the world. Histologically, the discrete lesions are identical.

It has been our opinion that the lesion produced by sericite, under a

similar experimental technique, should also be similar to that developing in miners exposed to sericite dust. If sericite is indeed the chief aetiological factor in producing silicosis, the experimental lesions produced by our method of introduction should be similar to those we developed when silica was used. Those lesions were strikingly similar to the silicotic lesions of man, and the histological unit of silicosis, the silicotic islet, was identical to that found in silicosis in man. Jones does not deny that silicosis could develop without sericite, but he insisted that in his studies sericite invariably was present. On the other hand, the South African workers do not deny the occurrence of sericite and other silicates in the rock of the mines of the Rand. Sayers (16), in a personal communication in July of 1934, says,

> Dr. E. H. Kittle, in his article on "The action of harmful dusts," presented last month before the Institution of Mining and Metallurgy calls attention to the fact that in the final report of the Miners' Phthisis Prevention Committee of South Africa, published in 1919, Dr. Watkins-Pitchford and Dr. J. Moir pointed out that the Rand ore contains sericite as well as other silicates, and they go on to say that probably a large proportion of the bright white images in a silicotic lung section of Rand origin are produced by sericite.

In our experimental work, however, we have been unable to develop, by the intratracheal injection of sericite, pulmonary lesions similar to those found in either the experimental animal or human subjects with silicosis. On the other hand, the lesions, and especially the residual fibrosis, are strikingly similar to those described by Badham (1) and by Simson (18), and had resulted from the long and continuous inhalation of harmful dusts other than silica. The fibrosis observed in our experimental animals was remarkably like that produced by nonsiliceous dusts in the human lung. We were able to produce experimental silicosis by injecting silica; we were unable to produce lesions even remotely resembling those of silicosis by injecting sericite.

SUMMARY

By using the same technique as was employed in studying experimentally the effects of different kinds of dust on the lungs of animals, we intratracheally introduced measured amounts of the mineral substance, sericite, into the lungs of rabbits; an immediate inflammatory reaction occurred, which was succeeded by very active processes of elimination. Sericite was removed by way of the air-passages and by the lymphatic

circulation. Residual sericite was retained within the lung and was found in the lymph nodes at the hilum of the lung. The residual sericite was contained within the protoplasm of phagocytic cells and the latter were identified as alveolar histiocytes. The phagocytic cells were grouped at the terminals of the alveolar ducts and along the course of the vascular and bronchial lymphatic structures. The "pleural drift" of Miller was demonstrated by the collection of phagocytes along the course of the interlobular vein and in the subpleural pulmonary tissue. Phagocytic cells were identified in the lumens of lymphatics at the periphery of bronchial lymph follicles, and also within the follicles themselves.

Masses of phagocytic cells, without distinct cell-membranes, were formed in the lymphatics as well as in lymph follicles of bronchial lymph nodes. These masses of cells occurred in various stages of degeneration and disintegration. Coincidently with the death of cells, sericite was set free, was again phagocytosed, and the process of elimination of dead and living phagocytes became continuous. Secondary lesions were formed and the lymph-spaces, alveolar spaces, and lumina of all the bronchial divisions contained cells in all stages of degeneration. After the third month following the introduction of sericite into the lungs, it was very rare to find any evidence of a lesion on gross pathological examination.

There was no evidence that a hyperplasia of phagocytes was stimulated, or that the individual cells were changed by metamorphosis into fibroblasts. Fibroblastic hyperplasia occurred, and produced a diffuse fibrosis involving the walls of all the finer bronchiolar divisions; and, extending locally by an interlacing of fibres, it involved the supporting connective tissues of the bronchi and vessels that were in the neighborhood of the lesion. The degree of fibrosis varied from a fine cobweb of interlacing fibrils to one in which all the pulmonary tissue was distorted and constricted by broad bands of dense, interlacing fibres that were without orderly arrangement.

BIBLIOGRAPHY

(1) BADHAM, C.: Notes on a fine type of pneumonokoniosis produced by silicilates and other minerals. In: Industrial hygiene: studies in industrial hygiene. (Extract from the report of the Director-General of Public Health, New South Wales, for the year ended 31st December, 1927), pp. 102–110.

(2) BADHAM, C.: Silicosis—Records of the International Conference held at Johannesburg, August, 1930, Geneva, P. S. King & Sons, Ltd., 1930, p. 61.

(3) BOHROD, M. G.: Pulmonary siderosis; two cases with reticulo-endothelial siderosis, Arch. Path., 1930, x, 179.

(4) CRONIN, A. J.: Dust inhalation by hematite miners, Jour. Industr. Hyg., 1926, viii, 291.

(5) GARDNER, L. U.: Pathology, human and experimental. In: Symposium on silicosis, Trudeau School of Tuberculosis at Saranac Lake, N. Y., June, 1934.

(6) GARDNER, L. U., MIDDLETON, E. L., AND ORENSTEIN, A. J.: Report on the medical aspects of silicosis, including aetiology, pathology, and diagnostics. In: Silicosis —Records of the International Conference held at Johannesburg, August, 1930, Geneva, P. S. King & Sons, Ltd., 1930, pp. 86–89.

(7) GEORGE, W. E.: Silicosis, Ibid., Geneva, P. S. King & Sons, Ltd., 1930, p. 39.

(8) GOADBY, K. W.: Quoted by Cronin.

(9) JONES, W. R.: Silicotic lungs: the minerals they contain, Jour. Hyg., 1933, xxxiii, 307.

(10) LEMON, W. S., AND FELDMAN, W. H.: The comparison of the development of the specific nodule of silicosis and of tuberculosis, Arch. Int. Med., 1934, liii, 367.

(11) LEMON, W. S., AND HIGGINS, G. M.: The development of the pulmonary silicotic nodule in the experimental animal, Amer. Rev. Tuberc., 1933, xxviii, 470.

(12) LEMON, W. S., AND HIGGINS, G. M.: Pulmonary lesions experimentally produced by intratracheal introduction of aluminum oxide and of borosilicate-glass, Ibid., 1934, xxx, 548.

(13) OSTERBERG, A. E.: Personal communication to the authors.

(14) POLICARD, A.: Le nodule silicotique pulmonaire, Presse Méd., 1932, ii, 1495.

(15) SAYERS, R. R.: Silicosis among miners, Bureau of Mines, Washington, 1925. (Quoted by Jones.)

(16) SAYERS, R. R.: Personal communication to the authors.

(17) SIMSON, F. W.: Silicosis in South Africa. A symposium on the histo-pathology, pathologic anatomy and radiology of the disease. In: Proceedings of the Transvaal mine medical officers' association, Johannesburg, October, 1930, p. 5.

(18) SIMSON, F. W.: Pulmonary asbestosis in South Africa, Brit. M. J., 1928, i, 885.

(19) SIMSON, F. W., STRACHAN, A. S., AND IRVINE, L. G.: Silicosis in South Africa. A symposium on the histo-pathology, pathologic anatomy and radiology of the disease. In: Proceedings of the Transvaal mine medical officers' association, Johannesburg, October, 1930, plates 1 to 8.

INVOLVEMENT OF THE SPINAL MENINGES AND OF BONE IN UNDULANT FEVER SIMULATING TUBERCULOSIS[1]

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There is a very extensive literature on brucella infection (under its various synonyms) in human beings in the United States and a still more extensive one abroad, the infection being an older acquaintance around the Mediterranean Basin; but a rather thorough search of all this literature reveals very few reported cases of brucella infection involving the meninges or bone and only one very questionable case in which there was involvement of both meninges and bone.

The cases cited below from these references exclude only those inconclusively diagnosed as meningitis due to brucella on the insufficient basis of headache, perhaps some suggestive neurological findings, and a positive blood agglutination for brucella; those inferred to involve bone-tissue on the basis of such complications as pain in the joints and articular swelling with or without effusion; and those of abscess-formation in the soft tissues alone, apparently not connected with any disease of bone. Some corroborative clinical or roentgenological laboratory procedures are considered as essential to the diagnosis.

In the American literature I found reported but 5 cases of meningitis due to brucella and one of bone involvement.

Sanders (1) reports a case with definite meningeal symptoms. The spinal fluid showed a few extracellular gram-negative pleomorphic organisms which grew well on North's medium; the cell count was over 300, with about 36 per cent lymphocytes; the pressure was increased. Cultures of the fluid were reported sterile after 48 hours and discarded. The meningeal symptoms did not disappear entirely for about four months. Other spinal-fluid cultures were made, and were reported negative. Some time later a spinal-fluid culture was made during a study at Johns Hopkins University and was reported positive for a probable brucella. The blood agglutination was positive for brucella (type not given) in a titre of 1–160. The spinal fluid continued to be cloudy, with increased pressure and an increased cell count. The patient was treated

[1] From the Medical Service, Walter Reed General Hospital, Washington, D. C.

with a polyvalent vaccine made from his own and other laboratory brucella strains. It was decided that the organism was of the porcine variety. The patient apparently made a satisfactory recovery.

Hansmann and Schenken (2) report a case of brucella infection of the meninges and mention 3 other conclusively proved similar cases. Nine other cases had been reported, but the diagnosis in each was dependent upon clinical observation and a positive blood agglutination, no organism having been isolated. The authors' patient died. *Brucella melitensis*, variety porcine, was grown from the spinal fluid. Injection of the spinal fluid into a guinea pig produced lesions in lymph nodes, spleen and liver, from which the original organism was recovered. Agglutination was positive in the patient, the titre not being mentioned. The spinal fluid contained 300 cells, with 36 per cent lymphocytes on one occasion and 271 cells, only 12 per cent of which were polymorphonuclears, on another occasion.

Kulowski and Vinke (3) have reported a case of spondylitis, due to *melitensis* (bovine variety), which was surgically treated. They mention a chronic, continuous low-grade elevation of temperature, without periods of remission, as a characteristic feature and pain, low in the back, as a frequent early symptom. At operation the interarticular facets of the 3rd lumbar vertebra on the right side showed a soft haemorrhagic joint, and a drop of pus appeared from the deeper structures. An abscess was found just anterior to the transverse process, from which about 200 cc. of thick pus escaped. Agglutination and skin tests had been positive for undulant fever. Blood culture had been negative. Culture from the pus yielded *Brucella melitensis*, bovine variety. The paper was written shortly after operation and the final outcome of the case is not known.

The foreign literature is little more prolific. Meningitis due to brucella is reported in four instances and disease of the bone in thirteen; while disease of both meninges and bone was found in one case.

DeSage, Pellerin and Vinerta (4) report a case of meningitic involvement in a girl of eighteen years who four months previously had had malta fever. Headache appeared about 15 to 20 hours after the subsidence of the fever, and later meningeal symptoms. Lumbar puncture showed 45 cells, all lymphocytes. Tuberculous meningitis, and later undulant fever were considered as aetiological factors. "The results of careful laboratory tests finally permitted the recognition of meningitis due to *melitensis* cocci and appropriate treatment was instituted." The nature of the diagnostic procedures is not given. After 14 days of treatment the patient had been relieved of symptoms. Another lumbar puncture showed 12 per cent polymorphonuclears and 68 per cent lympho-

cytes, the total cell count not being given. Later, cultures from the cerebrospinal fluid and injection into guinea pigs were completely negative. The patient developed a progressive paralysis of both legs, terminating in total flaccid paralysis; this was attributed to the formation of cicatricial bands; and penetrating ultraradio therapy of the dorsolumbar cord was given with such an excellent result that, after the second treatment, the patient began to move her legs and at the end of the treatment began to walk. (*Note:* This does not seem to be a proved case of *melitensis* meningitis and the rather miraculous recovery from a total flaccid paralysis following radiotherapy does not stimulate confidence. No Wassermann or agglutination of blood or spinal fluid is reported; nor any blood culture or blood count.)

Bingel and Jacobsthal report a case (5): A white male, age 32 years, with no previous illness of importance, developed meningeal symptoms. There was bilateral choked disc, and the blood Wassermann was negative. X-ray of the skull was normal, the sedimentation of the erythrocytes was slightly accelerated, and there was a slight leucopoenia with relative lymphocytosis. The cerebrospinal fluid was clear, with a positive Pandy and Nonne reaction and 290 cells, chiefly small leucocytes. The spinal-fluid Wassermann was negative. A blood culture was negative but the blood agglutinated *Brucella abortus* in a titre of 1–400. The condition remained stationary for a few weeks, with a fever of distinctly undulating character, and the protein reaction in the cerebrospinal fluid became more positive; the fluid gave a positive agglutination and culture for *Alcaligenes abortus*. The meningitis pursued a subacute course and at the time of the report was still present. The blood cultures were negative. The colloidal gold reaction resembled in many ways that seen in cerebrospinal syphilis.

Rouslacroix (6) reports a case, the patient becoming ill with what was first thought to be typhoid fever. The seroreaction was negative for typhoid and melitensis. The symptoms continued, and four months later the blood agglutination was positive 1–300 for melitensis and negative for typhoid. The patient was treated variously for melitensis with no benefit. Five months after onset of the condition he developed meningeal symptoms. Some pathological change in the right lung was noted also; and there was a history of a chancre, 35 years previously, with secondary skin lesions and iritis of the right eye. The Wassermann had last been positive 12 years previously and was again negative. Agglutination for typhoid was again negative, and agglutination of the blood positive for melitensis, 1–300. Lumbar puncture showed the fluid under pressure, 42 cells per cmm., practically all lymphocytes, and with a negative Wassermann. A third lumbar puncture, done nine months after the onset of illness, showed light yellow fluid of normal pressure with 45 cells per cmm., of which 91 per cent were lymphocytes and mononuclears. This spinal

fluid was negative for tuberculosis; the Wassermann was negative; the fluid, negative on culture, and agglutination for melitensis was positive, 1–150. A guinea pig, inoculated with the fluid, one month later showed at autopsy no evidence of tuberculosis. Meningeal symptoms soon reappeared severely. X-ray of the skull was negative. Eleven months after onset of the illness a decompression operation was done for a possible cerebellar tumor, with negative findings. Thirteen months after the onset of illness the patient was definitely on the road to recovery, and a month later a blood agglutination for melitensis was negative. Hospitalization was necessary, however, until eighteen months from the onset of the illness. The author thinks the condition was due to a double process of cerebrospinal meningitis set up by syphilis and ventricular ependymitis, this being ascribed to the dual aetiological factors of syphilis and melitensis, the one reënforcing the other. No blood cultures were done.

LeMaire (7) reports one case occurring in Algeria. There was a sudden onset, with symptoms suggestive of "grippe." Later, the patient had headache and symptoms of meningeal irritation: spinal puncture gave a clear fluid, with negative Wassermann and 225 lymphocytes, that was sterile on culture. The blood was negative except for a positive agglutination, 1–100, for melitensis. Meningeal symptoms became more severe and two more lumbar punctures were done for relief, but no report is given. Tuberculous meningitis was considered. On the 11th day after the onset of the nervous manifestations the blood culture was negative; while the spinal fluid showed 180 lymphocytes, a very rare polymorphonuclear, some increase in albumin and sugar, and its culture was positive for *Micrococcus melitensis*. The meningeal symptoms persisted, finally regressing slowly, with return to normal six weeks from their inception. Several other lumbar punctures were done; but no report of their study was made except that one month after the beginning of the meningeal manifestations there were still 200 lymphocytes per cmm. in the spinal fluid. A notable feature of the case was a persistently rapid pulse.

Roger (8) discusses spondylitis due to brucella. He quotes Cantaloube to the effect that the sacroiliac joint is the one most frequently involved. The author states that the joint involvement is generally a late manifestation. In only one of their cases was there a slight narrowing of the intervertebral space with an area of decreased density in the body of a lumbar vertebra. They noted in this case a thin film of bone, passing, over a period of three months, from the superior and inferior borders of the affected vertebra. In one of the cases there was more marked reaction, with several of the above described films of bone joining contiguous vertebra. The cerebrospinal fluid was normal in two cases. In the third there was an increase of albumin and "a slight lymphocytosis (5 cells per cmm. of spinal fluid)"; in the fourth case 25 lymphocytes per cmm. of

fluid were present; the Wassermann was negative in all. The agglutination reaction for melitensis in the spinal fluid was negative except in one case in which it was positive, 1–50. The author states that in all their cases the diagnosis was established by a typical clincal syndrome and positive agglutination, from 1–300 to 1–1000. He found the intracutaneous test positive in one case for melitensis and negative for tuberculosis. He mentions the long-drawn-out course of the condition coming on "habitually in the course of an infection which has already persisted for two to six or seven months." (*Note:* No definite description of any case is given. The number of cases reported upon is apparently four. No cultures were made; and there is no report in any specific case of abscess-formation, agglutination reaction or animal inoculation.)

Brun and Brunet (9) report a case of a female patient, 44 years old, in Tunis, who had used raw goat's milk all her life. She had a febrile disease considered as probably malta fever at the age of 17, although no laboratory tests were done. Two years later she had another febrile affection which lasted for 15 months. Following this she had three abortions within a period of 5 years. At the age of 38 years she had a third attack of fever, the symptoms being characteristic of malta fever. She refused to allow blood examinations but the clinical course was quite typical; the fever lasted for 2 months. Six months after this period of fever she noticed a small tumor at the left edge of the sternum in the 5th intercostal space. There were no active signs of inflammation. A radiograph made a few weeks later gave no information. Two months after the appearance of the tumor, incision was made and creamy pus evacuated. The internal portion of the tumor mass was "inserted in the sternum"; the edge of the sternum was curetted, but no sequestrum or definite evidence of osteitis was found and the condrosternal articulations appeared to be normal. Healing was slow, requiring six weeks. Cultures from the pus gave a pure culture of an organism with all the characteristics of *Micrococcus melitensis*, which was agglutinated repeatedly with a 1–300 dilution of an antimelitensis serum, but not by the patient's serum. (*Note:* Disease of the bone was not evidenced here either by X-ray or at the time of operation.)

Weil (10) describes briefly a case of Bang's infection, proved by agglutination reaction (titre not given). The fever disappeared after three weeks, and three weeks later, without fever, there was swelling of the dorsum of the right foot, accompanied by pain and a bluish discoloration. The agglutination for Bang's was reported as strongly positive. The author reports that there was no indication of tuberculosis, syphilis or gonorrhea. A radiograph showed bone atrophy and haziness of the joint between the cuneiform and metatarsal bones. There was no definite evidence of actual bone involvement, either clinically or by X-ray. (*Note:* No cultures were made from any source. There was no

evidence of abscess-formation. The blood count and other laboratory procedures are not given; and the details of the case are not sufficient to justify, it would seem, a positive diagnosis of melitensis infection of the bone.)

Cuatrecasas (11) reports a case as probably one of malta fever with spontaneous fractures. The patient complained of pain, distress and stiffness in the cervical region on movement, anorexia and bronchial catarrh. Physical examination showed enlargement of the liver and spleen; inguinal and axillary adenopathy; exaggeration of the tendon reflexes in the lower extremities; an undulating and irregular type of fever; a mild secondary anaemia; leucopoenia with low polymorphonuclear count; sweating nocturnally and diurnally; loss of weight; pain in various joints; abundant mucopurulent expectoration; long duration of the disease (more than a year); and negative agglutination for brucella on two occasions. No blood cultures were made as the patient refused them. Indolent swellings, the size of a hen's egg, appeared over various areas of the chest; puncture revealed them to be of the character of a haematoma. Later, several spontaneous fractures of the ribs occurred, each corresponding to one of the above mentioned swellings. No radiograph of the bones was made. (*Note:* Although this is reported as a case of spontaneous fractures and probable malta fever, the connection with brucella infection does not seem to be established, as agglutinations were negative and no blood or other cultures were made. A Wassermann was not given. Animal inoculations were not done, nor X-ray study made of the bones. The clinical course is suggestive of malta fever.)

Casaneuve (12) cites a case of osteoperiostitis occurring during melitensis fever. His patient developed melitensis from drinking goat's milk, and, as a complication, pleurisy with effusion, left. Later, there were several joints involved in such a way as to resemble "a chronic rheumatic infection." About three months from the beginning of his trouble the patient began to have acute inflammatory swellings, red and tender, first in the bones of the lower extremities and later in other areas, extending over a period of four months. Following the acute stage each swelling went on to an exostosis of the underlying bone. At a later period there was a recrudescence of the condition in the bones and joints of both legs. There was no suppuration at any time. Nine months subsequent to the beginning of the illness, agglutination for *Brucella melitensis* was found positive (titre not given). The condition lasted for about twenty months altogether. The radiograph showed only the exostoses. The Wassermann was negative. Cultures of the blood and urine were negative for *Brucella melitensis*. The author quotes Cantaloube as having seen 9 such instances out of 172 cases of Mediterranean Fever. He also states that Gillot saw such a case in Algeria, Pochas one in Athens, Pieri one in Rome, and Brault one in Algeria, the latter's case going to autopsy. (*Note:* Does not seem to be a proved case of brucella infection.)

Clerici (13) reports a case that had undulant fever, confirmed by positive agglutination, 1–1000 titre, and a positive blood culture for brucella, variety melitensis, a typical clinical course and its persistence over a long period in spite of various treatments. The patient was a doctor who contracted the infection in handling a culture of brucella in the laboratory. There was a mild secondary anaemia with a normal white count. Good results with an autogenous vaccine were obtained. Eight months after the inception of the disease there was a return of symptoms, with fever, chills, sweating and enlargement of the liver and spleen. Agglutination was positive for brucella in 1–1000 titre; blood culture was negative, and leucopoenia present. One month later the patient began to have lumbosacral pain, radiating into the legs, rapidly increasing in intensity, and increased by standing, coughing or sneezing. Physical examination showed little other than the enlargement of the liver and spleen and rigidity of the lumbar spine. There was no particular pain on pressure. Neurological examination was not significant. Radiograph of the lumbar spine showed no pathological change. The condition was considered a lumbar arthritis due to undulant fever, and a "corset" was provided. Heliotherapy was noted as part of the treatment. Three months later a radiograph showed incipient bone lesions in the 4th and 5th lumbar vertebrae. The pain was still present, as was the fever. Another radiograph twelve days later showed vacuolization of the left articular process between the 4th and 5th lumbar vertebrae and also involving the body. The patient did very well under treatment for the next 11½ months when, without apparent cause, there was a return of the severe pain in the back, with increase in temperature, some chilling, a few sweats and enlarged liver and spleen. The blood-serum agglutinated positively at 1–500. The fever lasted for only about one week, and the pain was gone in a month. The patient returned to work two years and seven months after the onset of the illness, wearing a "corset." A radiograph about this time showed a diminution of previous changes but with proliferation of the bone from one vertebra to the other.

Lassen (14) reports the case of a man of 59 years, who had previously had an attack of fever lasting two weeks, with no particular symptoms, but blood agglutination was positive for *Brucella abortus*, 1–800. Two months later he had pain and muscle cramps in the loins bilaterally and was in bed for six weeks. At this time a radiograph showed mild changes of spondylitis deformans of the lumbar and lower dorsal vertebrae. Symptoms five months from inception of the fever were worse, and pain was localized between the spine and right iliac crest. The patient was furnished a brace for the back, but pains continued in spite of fixation. There was no vertebral tenderness, but the pain was severe at the site of the 1st and 2nd lumbar vertebrae, especially on motion. There was no evidence of abscess-formation. The white blood count was 10,000,

with a normal differential; Widal negative; and agglutination positive, 1–200 for *Brucella abortus*. A radiograph, six months after the beginning of the patient's illness, showed a destructive disease of the intervertebral disc between the 1st and 2nd lumbar vertebrae, with narrowing of the intervertebral space and condensation of the bone at the contiguous surfaces of the two vertebrae; active bone-formation; and contour of the vertebrae hazy. The aetiological factor was considered to be tuberculosis. About three weeks later there was distinct tenderness over the spinous processes of the 1st and 2nd lumbar vertebrae. Radiograph, six weeks subsequent to the one last-mentioned, showed clearing; at the same time, new bone-formation was evident along the sides of the affected vertebrae with almost a bony bridge on the right side. A radiograph two months later showed no change. The treatment had been rest on a flat hard surface. Nine months after the beginning of his illness the patient was able to sit up on the side of the bed without pain and without support, and a week later was up in a leather "corset" on ambulatory treatment. His temperature had been normal throughout his stay in the hospital (3 months). Another radiograph showed narrowing of the intervertebral space to 1.0 to 2.0 mm. but no evidence of destructive process of the bones; ossification was more advanced and new bone present on both sides and the anterior surface of the affected vertebrae. The patient had entirely recovered 16 months after the beginning of the illness. The author's conclusions are that the patient had a *Brucella-abortus* infection 6 months before coming to hospital and at least two months before the back symptoms developed. (*Note:* There was no abscess-formation in this case; no cultures were made; no animals inoculated; no X-ray of the lungs for tuberculosis; no Wassermann done; but the diagnosis of spondylitis due to brucella seems logical.)

Jensen (15) had a case of spondylitis due to *Brucella abortus* in a boy 17 years of age who entered the hospital complaining of a painless swelling in the left inguinal region of one month's duration. The patient was in good general health and physical condition, with a fluctuating mass the size of an orange in the left inguinal region and extending into Scarpa's triangle. He had no tenderness on pressure over the spine, and his temperature was normal. The first impression was tuberculous spondylitis with psoas abscess; but the radiograph did not resemble tuberculosis, and was considered an infectious spondylitis of the 3rd and 4th lumbar vertebrae, most probably typhoidal in origin. The patient, one year previously, had been in a hospital one and one-half months for a febrile condition. No adenopathy or splenic enlargement was noted, no skin rash, no pathogenic bacteria in urine or stools. A Widal was negative fourteen days after onset of illness. Three or four months later pain developed across the loins. A radiograph of the back was negative and the pain disappeared shortly. Widal and Wassermann negative; and Pirquet

positive. While in hospital the left inguinal abscess was punctured and drained three times. The pus never contained *Bacillus typhosus* and was negative after culture and guinea-pig inoculation. After four months of treatment the abscess had disappeared, but another one appeared on the right side, this disappearing spontaneously without puncture after ten months, and a radiograph reported a decided improvement in the condition of the lumbar vertebrae. Another Widal was negative and the patient's blood-serum agglutinated Bang's bacillus up to 1–100 and gave a plus complement fixation for the same organism. Two weeks later a similar result was obtained on a second specimen. Blood cultures were negative. Injections of blood and urine into guinea pigs were negative. Eleven months after entrance into the hospital there was no apparent abnormality of the spine, and the patient was discharged wearing a body brace. Five months after discharge he was without symptoms and working, and a radiograph showed the process in the lumbar vertebrae to be consolidated. The author argues against a diagnosis of tuberculosis or typhoid fever: against tuberculosis because of the negative history of tuberculosis, the X-ray picture, the negative cultures and guinea-pig results and the too rapid recovery for tuberculous spondylitis; and against typhoid spondylitis were the negative Widals and culture of the stool and pus, and the absence of a history of typhoid fever. The author's arguments for abortus infection were history of febrile illness, the fact that the patient had worked on a farm and handled cattle, drank raw milk, and two years after exposure showed 1–100 agglutination for Bang's bacillus. (*Note:* This case is well worked up, and, although all cultures were negative for brucella, the responsibility of this organism, by exclusion of other factors at least, seems established.)

Redell (16) had a case of spondylitis occurring as a complication of undulant fever, which was under observation and treatment for a couple of years. After lifting a heavy weight, this patient, a young man, was confined to bed with pain in the back. On the 11th day he developed fever, chills and headache in addition to the back pain. The lumbar muscles on the left side were very sensitive to pressure. There was some elevation of temperature and pulse with slight stiffness of the neck. Lumbar puncture showed an elevated spinal-fluid pressure, but was otherwise negative. The Widal was negative, but a few days later the blood agglutination was found positive for Bang's bacillus. After approximately a month the temperature returned to normal, but the pain in the back continued. There were no symptoms of meningitis. Diagnosis of rupture of the loin muscles was made. Symptoms disappeared for about two months and then returned. A radiograph showed a haziness in the lower portion of the body of the first lumbar vertebra, with bony deposits bridging over the intervertebral space; there was considered to be an inflammatory

process in the 1st and 2nd lumbar vertebrae and of the intervertebral disc between them. A month later the Pirquet test was negative, the pain and tenderness in the upper lumbar region (the pain being increased by motion) continued, and the patient was put in plaster. The precipitation reaction of the blood had increased from 5.0 mm. an hour three weeks previously to 20.0 mm. an hour, and the intracutaneous test was negative. Two weeks later the agglutination for Bang's bacillus was still positive (titre not given). A radiograph about eight months after the beginning of the trouble showed the intervertebral space between the 1st and 2nd lumbar vertebrae to have decreased since the previous examination. Destruction in the bodies of the vertebrae had increased and the deposits were larger. The precipitation reaction now 33.0 mm. an hour. Subjective symptoms began to diminish; radiograph two months later showed conditions unchanged. After four months the plaster-of-paris support was replaced by a "corset." The temperature and pulse had been normal throughout this time. The patient was now up and felt well, and the precipitation reaction began to show normal values. Agglutination for Bang's bacillus was positive (titre not given), but that for typhoid and paratyphoid bacilli was negative. Nineteen and one-half months after the inception of the trouble the patient was reëxamined, was feeling well, and agglutination for Bang's bacillus was positive (titre not given). Seen again two years from the beginning of the disease, he considered himself completely cured. There was no limitation of motion; the radiograph showed the intervertebral space narrowed as previously; and the outlines of the bones were sharply defined. Two and one-half years after the beginning of the illness his agglutination was still positive for Bang's bacillus. Wassermann negative. The patient was known to have used milk from a herd in which infectious abortion had occurred, and the author feels that the first symptoms were caused by a Bang's infection. The bony changes he considers due to an inflammatory process, also due to Brucella. (*Note:* There was no abscess-formation. There were no blood or urine cultures and no animal inoculations made; the case appears to have not been satisfactorily established as due to brucella.)

Botreau, Roussel and Huord (17) had a case of spondylitis due to brucella, with sacroiliac arthritis and bilateral abscess of the buttocks resembling cold abscesses. The patient was a young soldier who had had two previous injections of typhoid vaccine, including the paratyphoid A and B strains. He entered the hospital because of a continuous fever, a bilateral bronchitis, constipation and palpable spleen, symptoms which suggested a diagnosis of typhoid fever. Sero diagnosis tests for typhoid, paratyphoid A and B, and melitensis, were positive for paratyphoid B only. He improved for several days; then there was a recrudescence of fever and a swelling appeared in the right buttock. This was about one month after the beginning of the disease.

Agglutination for *Micrococcus melitensis* was positive, 1–400. The temperature persisted, being of an undulating nature. Some time later, the swelling of the right buttock not having diminished, the left buttock showed a similar swelling, extremely painful; these swellings persisted, but the tenderness and temperature decreased and the patient was allowed to leave the hospital, three and one-half months after the beginning of the disease. He reported later in very poor condition, having lost a great deal of weight. His appearance now was that of a tuberculous patient. Examination of the chest and abdomen was negative, but the right buttock was distended by two large "cold" abscesses which appeared to communicate with eath other. There was a similar but smaller abscess on the left buttock. He complained of pain in the sacroiliac region and lumbar spine. Tenderness was most marked over the left sacroiliac joint and 5th lumbar spine; rectal examination was negative; X-ray of the plevis did not furnish much information. The abscesses were punctured, and each was injected with lipiodol for radiographic purposes. A stereo X-ray showed that the superior pole of the right abscess went above the iliac crest and sacrum and came into contact with the side of the 5th lumbar vertebra. The radiographic aspect of this vertebra was normal. The lumbosacral joint appeared normal. Direct examination of the pus, and cultures, showed no organisms. Guinea-pig inoculation was negative at the end of three months. Several cultures taken during the febrile period remained negative. Agglutination was positive for typhoid, 1–100; paratyphoid A, 1–200; paratyphoid B, absolutely negative; and melitensis, 1–200. The cutaneous tuberculin test was strongly positive. The first positive agglutination for paratyphoid B was considered of doubtful value. The abscesses required repeated puncture; the treatment was with melitensis vaccine. Six months after the beginning of the disease, the patient's general condition was excellent with return of normal weight. At no time was the spinal fluid abnormal, nor did it give a positive agglutination for melitensis. The patient was entirely recovered nine and one-half months after the beginning of the illness but the serum agglutination for melitensis persisted strongly. (*Note:* Although the Wassermann is not given and all cultures were negative, the responsibility of a brucella infection for the bone changes may be admitted.)

Brault's is the only case (18) reported in the literature of both meningeal and bone involvement. This was a woman, 45 years old, who entered the hospital with gonorrheal urethritis and metritis but who, in addition, had had a fever for about fifteen days. She complained of cough and had a temperature between 100.4° and 102.2°. It became normal in five days, but after a two-day interval returned for about three weeks. During this period the patient had articular pains in the left wrist and right knee and in the left thigh and leg. There was normal temperature for about three weeks, and again the fever returned with severe pain in the left thigh, which became swollen; the swelling

began immediately above the epiphysis and involved the entire lower half of the femur. The bone seemed increased in size, and the area was red, shiny, hot, and tender. Later there was involvement of the tibia on the same side. The patient had profuse perspiration, and diarrhoea for several days. Pain in the femur and tibia continued. The author considered operation but made a diagnosis of malta fever and decided to wait. Pain diminished in about a month but tenderness and swelling persisted. A seroreaction for malta fever was positive. Two or three weeks later there was another exacerbation. The patient was given 25 cc. of immune horse-serum, following which her temperature became normal. A short time later swellings were noted in the left temple, on the apex of the cranium and above the right mastoid region. One of these became fluctuant and was punctured, a few drops of pus being obtained, and staphylococcus was recovered on culture. The others were punctured but no pus was obtained. Three weeks later the patient's condition became much worse and there were signs of meningitis. Lumbar puncture was done and the fluid was cloudy. The patient died about two days later. At autopsy a small amount of pus was found in the cranial swellings, and there was a diffuse superficial osteitis of the involved bones. Pus was found between the dura mater and the cranium. There was suppuration of the right lateral sinuses with thrombophlebitis. The femur showed osteitis in its lower half and, while the bone was friable, no pus was found. Similar lesions were found in the left tibia. (*Note:* There does not seem to be enough to support the findings of brucella as the responsible factor in this case. One would certainly think first of a gonorrheal arthritis, with possibly a gonococcus septicaemia later. There was apparently only one seroreaction for brucella and, while positive, the titre is not given. No cultures were made of the blood or urine, and the finding of only staphylococci in the pus is suggestive of some other source for the infection. There was no Wassermann; no animal inoculation; no spinal-fluid study or culture; no X-ray study of the diseased bone; and no blood count; all of which would have been indicated to establish the diagnosis.)

The cases reported in the American literature are acceptable. Of those in the foreign literature, that of DeSage, Pellerin and Vinerta (4) seems unproved as *Brucella meningitis;* those of Brun and Brunet (9), Weil (10), Cuatrecasas (11), Casaneuve (12) and Redell (16) are not clear-cut cases of bone disease due to brucella; and that of Brault (18) is extremely unlikely to have been a combined meningeal and bone involvement of melitensis origin. This leaves then 8 cases of meningitis, 9 cases of bone involvement and no cases combining both meninges and bone.

It is quite possible that some references in the literature have been

missed; also, other such cases have certainly occurred and were not reported. Such complications of brucella infections are, undoubtedly, far more common than is realized.

There has been observed in the Walter Reed General Hospital, over a period of more than two years, a case with involvement of the spinal meninges and of the lumbosacral joint, which is considered the result of infection by *Brucella melitensis*, bovine type. The case is reported here in considerable detail.

CASE REPORT

C. C. E., white male, age 49 years; officer, Military Service, since 1905. Admitted to Walter Reed General Hospital on February 18, 1932. *Family history:* Unimportant. *Previous personal history:* Had usual diseases of childhood without complications; dengue fever 1906 and 1910. Infection of undetermined origin in the right leg, 1910, with secondary infection of the right inguinal lymph nodes leading to suppuration; operated upon with satisfactory recovery. While roller-skating in 1919, he wrenched his back; the next day, while walking on the street, he was suddenly seized with a pain in the back, so severe that he fell to the sidewalk; was taken to a hospital where a diagnosis of sacroiliac strain was made; the pain disappeared after one day; he left the hospital and had no further trouble. Tonsillectomy, 1921. In 1924 he was ill for about a week with pain in the back, the condition being diagnosed as lumbago. Had submucous resection in 1926, and puncture of the right maxillary sinus several times in 1931, and sinusotomy, same sinus, in 1932 for suppurative sinusitis. Venereal disease denied. Has always been very strong, active and athletic.

History of present disease: Was in his normal health until December 24, 1931, when he developed a head-cold. By evening had aching along entire spine and extending into shoulders. That night felt that he had a rather high fever and later there was profuse perspiration. These symptoms persisted, so that he called a doctor, December 27, who treated him for influenza. Was in bed for one week; felt improved and went to duty on January 2, 1932. Was still having some fever in the late afternoons and marked sweating at night. These symptoms persisted, but he continued, with considerable effort, to do duty until early in February, 1932, when he again was ill at home for three or four days. Went back to work again, but felt as though he had some fever in the afternoons. On February 15, 1932, he noticed for the first time pain in the lower back, location somewhat indefinite, but it was not severe; and he decided it was "lumbago" which he had had previously and for which he had been treated by an osteopath with good results. On February 17, 1932, he visited a chiropractor and had an "adjustment." That night he was awakened by

the severity of the pain which by the next morning had become throbbing in character; this pain in the lower lumbar region continued to be so severe that he called a doctor and was sent to the hospital on the evening of February 18, 1932. He was admitted to hospital as a litter case, his only complaint being that of severe pain in the sacroiliac region, bilaterally; more on the right and increased by pressure. Temperature 99.2°, pulse 98, respirations 22, white blood count 12,000 with 90 per cent polymorphonuclears. (*Note:* Some time later, after it had been decided that his illness was due to infection with brucella, this officer gave the additional history that he had always been very fond of milk and drank one to two quarts of it daily. He did not care for pasteurized milk, and for about eighteen months before the beginning of his illness had been drinking unpasteurized milk which he obtained specially for that purpose.)

Physical examination on admission: Height 72 inches, weight 195 pounds stripped (patient's statement); in good general condition; well nourished and developed; special senses normal except for error of refraction corrected by lenses; skin showed marked generalized ichthyosis; mucous membranes clear and of good color; tonsils out; no adenopathy; thyroid normal; no varicosities; some palpable sclerosis of the superficial vessels; blood-pressure, systolic 110, diastolic 70 mm. Hg; heart, lungs and genitalia normal; abdomen normal in contour, soft; liver palpable on deep inspiration; spleen not felt; no masses or other abnormalities noted; pupillary, skin and tendon reflexes normal; Babinski negative; muscles and joints normal; osseous system negative except for pain on pressure over the right sacroiliac joint.

Tentative diagnosis: Sacroiliac arthritis, acute, cause undetermined, probably aggravated by chiropractic treatment.

It is more convenient to describe the progress of this case over the ensuing period of two years and three months by dividing it into five stages: (1) that prior to the meningeal involvement (2 months); (2) that during the meningeal involvement (4½ months); (3) that intervening between termination of the meningeal involvement and the definite evidence of bone involvement (4½ months); (4) the stage of active bone involvement (5 months); and (5) convalescence (10½ months), after which he returned to his usual occupation.

First Stage: February 18 to April 17, 1932

Immediately upon admission he was placed on a hard bed, given physiotherapy in the form of baking, and symptomatic treatment. A notable feature of the case was constipation. Gradual improvement took place, although the constipation and pain in the back persisted, the latter causing insomnia. By the middle of April, 1932, the patient had visited some of the clinics in a wheel-

chair. The diagnosis of sacroiliac arthritis did not seem tenable. There was now marked tenderness over the left sacroiliac region and in the lumbosacral spine, and any movement increased the muscle spasm and pain; also, there had been considerable loss of weight and there was persistent pain and tenderness of the right testicle, though with little actual swelling; later this was also present in the left testicle. Dental X-ray had shown one nonvital tooth with periapical disease, and this had been extracted. Proctoscopic examination showed a slight uniform hypertrophy of the prostate; the rectal mucosa was normal. The nose and throat examination disclosed no evidence of sinus involvement, although the patient previously had been troubled in this manner. The eyes, including the media and fundi, were negative. Radiograph of the lumbar spine, pelvis and hip-joints had been negative other than for a rather marked demineralization of the bones, and radiograph of the sinuses revealed only haziness, considered due to thickened membrane. A gastrointestinal series and barium enema had been negative. A cholecystogram showed two stones in the gall-bladder, but there were no symptoms referable to these. By radiograph the heart and lungs were negative. Several urines had been negative, including culture from the gladder and from each kidney. The stools had been negative for parasites and ova, and cultures were negative for haemolytic streptococci and for *Entamoeba histolytica*. The blood count indicated only a mild secondary anaemia and the whites had ranged from 16,500 with 74 per cent polymorphonuclears to 6,500 with 56 per cent polymorphonuclears. Blood Wassermann and Kahn were negative. Uric acid was 3.6 mgm. per 100 cc. of blood and the complement fixation test for amoeba was negative. Blood calcium was 13.39 mgm. per 100 cc. of blood-serum. Prostatic massage, smear and culture were negative, as was cystoscopy with ureteral catheterization. The temperature had been elevated to 102°F. in the afternoon for the first two days in the hospital; and was then normal for the ensuing period of four weeks; then irregularly elevated to 100° plus F., in the afternoon for two weeks; then normal for six days. On April 10, 1932, another elevation of temperature began, reaching a peak of 105°F. on April 19, and gradually declining to normal by April 25. The pulse was not remarkable, being proportionate to the temperature.

Treatment: Throughout this stage had been physiotherapeutic and symptomatic. The diet was of the high-vitamine, high-calory type and calcium lactate was given in view of the X-ray findings of demineralization of the bones and the high blood calcium.

Second Stage: April 18 to September 7, 1932

On April 17, 1932, being just beyond the peak of the temperature-wave noted above and with a temperature at the time of 103.2°F., the patient was noted to be slightly stuporous, irritable and incoherent. He denied any headache, as

he did insistently throughout his illness. These symptoms increased, and, April 18, a spinal puncture was done for diagnostic purposes. The Wassermann was anticomplementary in the first two dilutions and negative in the weaker dilutions (1.0, 0.5, 0.25 and 0.1 cc.); there were 2,270 cells per cmm. of fluid, of which 1,470 were red cells and 800 whites, with a differential count of 28 per cent polymorphonuclears and 72 per cent mononuclears; the colloidal-gold reaction was 0001110000; no organisms were found on smear or after gram-stain; cultures on blood plate and broth were negative after 48 and 72 hours, respectively. Another spinal puncture, April 20, showed the Wassermann again anticomplementary in the first two dilutions and negative in the two weaker dilutions; the cell count was 990 per cmm., 875 being red cells and 115 white cells; the colloidal-gold reaction was 1112221000; no organisms were found on smear and the culture was negative after 24 hours. The urine showed single-plus albumin and an occasional granular cast. The white blood count was 6,500 with 70 per cent polymorphonuclears. Blood chemistry showed sugar 140.8 mgm., and urea nitrogen 13.5 mgm., per 100 cc. A blood culture taken on April 20th was negative after 240 hours. Severe pain in the back was the only prominent subjective symptom and the patient was perspiring freely nocturnally. On April 24, 1932, there was retention of the urine, requiring catheterization twice each 24 hours for the ensuing week. Examination of the ocular media and fundi was negative. Roentgenogram of the dorsal and lumbar spine, sacroiliac and hip joints was negative. Spinal puncture, May 2, showed the Wassermann negative throughout; there were 226 red cells and 454 white cells per cmm. of fluid; the differential count showed 1 per cent polymorphonuclears, 2 per cent large lymphocytes, 97 per cent small lymphocytes; the globulin was strongly positive; the colloidal-gold reaction was 2455543331; no organisms were noted on smear. A guinea pig inoculated with the centrifugated sediment from the fluid was killed six weeks later and no evidence of tuberculosis or any other pathology was noted. (*Note:* About this time there was an unfortunate occurrence. An agglutination of the blood for the brucella group had been requested and information received that it was negative. This caused us to dismiss for some time the possibility of brucella as an aetiological factor in the case in spite of the several suggestive features (type of temperature; marked sweating; rather generally normal white blood count; orchitis; constipation; apparent elimination of syphilis, tuberculosis and other agencies). It was found later that the agglutination had not been run.)

During the remainder of this stage seven more spinal punctures were done; the Wassermann was always negative and the cell counts were as follows: May 17—red cells 18, white cells 87 per cmm. of fluid, with a differential count of polymorphonuclears 8 per cent, lymphocytes 75 per cent and degenerated cells 17 per cent: June 22—red cells 1354, white cells 146; differential count, 100 per cent lymphocytes: July 5—red cells 165, white cells 26; differential count,

lymphocytes 92 per cent, polymorphonuclears 8 per cent: July 15—red cells 622, white cells 28, mononuclears 92 per cent, polymorphonuclears 8 per cent; July 29—red cells 1, white cells 13, mononuclears 42 per cent, polymorphonuclears 58 per cent: September 7—red cells none, white cells 6, all small lymphocytes. In these specimens the glucose content had been found normal in five; globulin and albumin were noted as being heavily positive in three but only showing a faint trace in the last specimen. The colloidal gold had a meningitic type curve in all save the last specimen when it was flat. Smear for organisms had been negative in five of the specimens, the stain being with acid-fast and gram stains. A guinea pig inoculated with the centrifugated sediment from the fluid taken May 18 died on June 8, 1932; autopsy showed no pathological changes of any nature. Two other guinea pigs, inoculated with the sediment from the spinal fluid and placed, one on a scurvy diet and one on a regular diet and carried until their death on August 30, 1932, showed no evidence of tuberculous infection. Culture of the spinal fluid done with three specimens was negative after variable periods. The pressure of the fluid on each puncture remained about 11 to 12 mm. with no evidence of blocking. (*Note:* In more than half of the punctures blood was obtained with the spinal fluid. The blood was definitely not from the spinal canal but due to a considerable inflammatory reaction in the tissues punctured by the needle. Obviously, however, the white cells were present in each specimen in such a markedly increased proportion to the red cells, and the white cell differential count varied so greatly from that of the blood at the time, that their origin almost entirely from the spinal canal cannot be questioned.)

Four complete neurological examinations during this stage had failed to show anything definite or helpful. The possibility of syphilis, tuberculosis and encephalitis was discussed, but none of these was considered a tenable diagnosis.

The blood-pressure continued normal during this stage. Two other roentgenograms, at monthly intervals, of the lumbar spine and pelvis were negative. The urine for a time after the retention and catheterization contained many white blood cells and single-plus albumin, the specific gravity remaining within normal limits and the measured output being normal. Cultures of catheterized specimen gave *B. coli* on two occasions, for which proper treatment was instituted. The blood picture did not vary a great deal, continuing to show a mild secondary anaemia, with red counts ranging around 4,000,000 to 4,800,000, haemoglobin 75 to 85 per cent, and a white count rarely exceeding 10,000, frequently below 9,000 and occasionally as low as 4,500; the polymorphonuclears were at no time above 82 per cent, this being on only one occasion, the counts generally being below 75 per cent. Five provocative blood Wassermanns and Kahns were negative. Seven blood cultures were negative, six of them after a seven-day interval.

The patient remained a bed-case. The temperature range from the end of the wave on April 19, 1932, continued within normal limits until June 2, 1932; following this until the end of this stage there were irregular daily elevations, highest in the afternoon, generally 99° to 101°F., but with several indefinite undulations of higher and lower temperature.

Treatment: During this period was largely symptomatic. However, mixed treatment (mercury and potassium iodide) was given by mouth for a considerable part of the time. The patient's bed was wheeled on to the sun-porch for daily sun baths for periods up to one hour and he was given a course of sodium cacodylate (12 injections) hypodermically.

There had been no symptoms whatever, subjectively or objectively, of meningeal involvement after the first spinal puncture. The complaints were always the same,—of pain in the lumbosacral region, some times in both sacroiliacs, and radiating to the hips. This pain was aggravated by jarring and by coughing or sneezing. Constipation continued to be present and there was marked loss of appetite. The weight had dropped to 151 lbs.

Third Stage: September 8, 1932 to January 17, 1933

The genitourinary infection with colon bacillus proved stubborn, and the patient during most of this stage was receiving treatment for this condition in the form of urotropin with ammonium chloride and acriflavine with alkalies, alternately. Lumbosacral pain continued about as before. Roentgenograms of the lumbar vertebrae and entire pelvis for bone involvement were being made at monthly intervals, but not until December 19, 1932, was any abnormality noted; at this time there were definitely irregular areas of bone condensation in the last lumbar vertebra and upper portion of the sacrum. The lumbosacral joint was hazy and blurred. The appearance was suggestive of an intense inflammatory reaction in this area. (See figures 1 & 2.) Physical findings unchanged. Spleen never felt. The patient had developed a cough, paroxysmal and moderately severe, of which he complained bitterly as the jar caused sharp pain in the lumbosacral region. Physical examination and radiographs of the chest were negative. The afternoon elevation of temperature continued, but was generally below 100°F. Blood-pressure was normal. Nutrition improving and strength good. Continued a strict bed-case. About December 1, 1932, the temperature began to rise and, while the maximum was generally 101°F., there were occasional elevations to 102°. Some tenderness was developing to pressure over the lower lumbar spine, without definite localization; the throat and larynx were negative. Cystoscopy and ureteral catheterization were negative. The blood picture continued as previously during this stage, that is, there was a mild secondary anaemia, the white count being generally normal but with occasional elevations as high as 15,000; and the polymorphonuclear count always within normal limits.

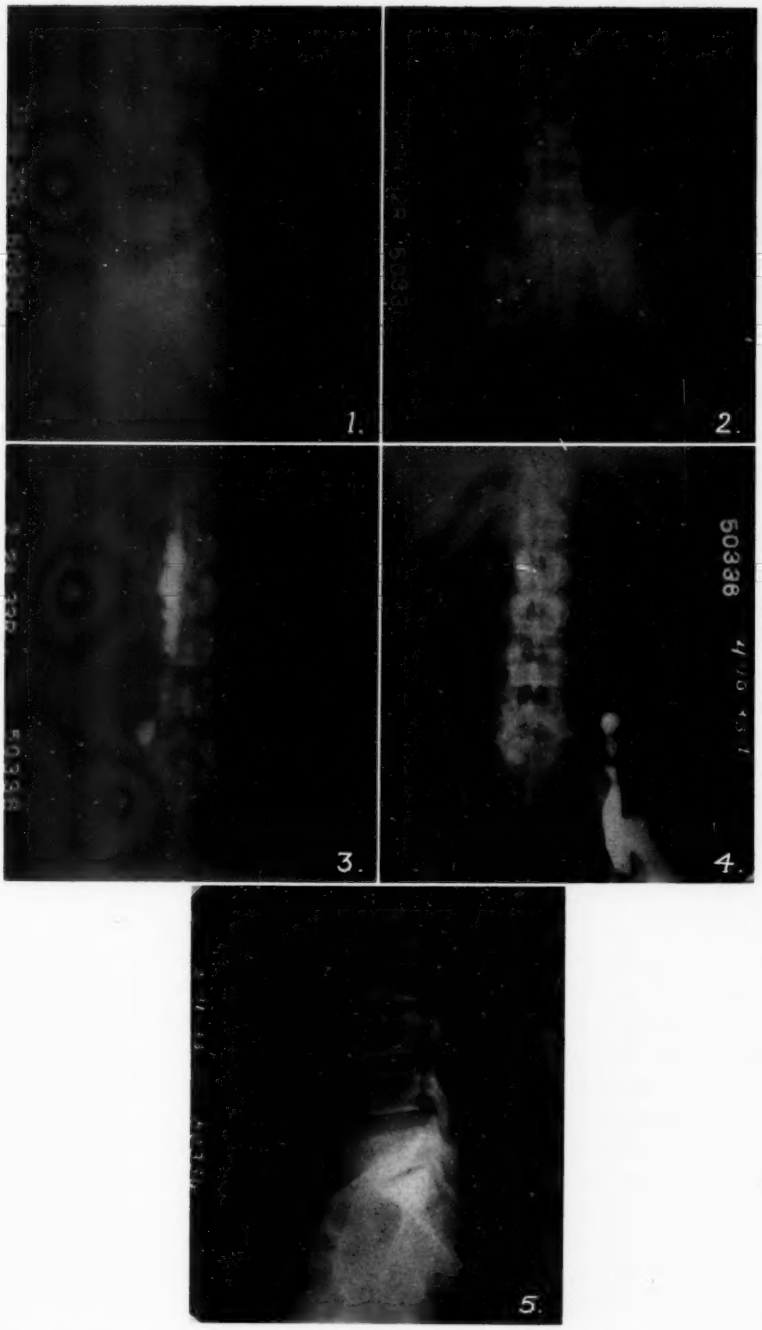

FIG. 1. Lumbosacral joint is hazy and gives appearance of intense inflammatory reaction. There are areas of bone condensation in the contiguous bone structures.

FIG. 2. Same as fig. 1. Anteroposterior view.

FIG. 3. Lipiodol in soft tissues following injection of dorsal abscess. Injected above, it has passed downward along a sinus leading to region of the lumbosacral joint.

FIG. 4. Lipiodol injection of left psoas abscess from below.

FIG. 5. Definite bony bridging between 5th lumbar vertebra and sacrum. Inflammatory reaction in lumbosacral region much decreased.

Blood agglutination for brucella was repeatedly positive during this stage, ranging from 1–160 to 1–320. Complement fixation with *Brucellà-abortus* antigen was four plus in 0.20, 0.15, 0.10 and 0.05 dilutions of serum. Complement-fixation titration for brucella-type determination resulted in the serum proving of higher titre with the bovine than with the porcine and melitensis types. Complete fixation of complement occurred with as little as 0.005 cc. of serum with the bovine-type antigen, whereas with the porcine and melitensis types the smallest amounts of serum giving complete fixation of complement were 0.07 and 0.05 cc. respectively. Agglutination absorption test showed the agglutinins in the blood-serum completely absorbed by *Brucella abortus* (bovine type) and only partially absorbed by *Brucella abortus* (porcine type) or *Brucella melitensis*. The test was thus positive for the *Brucella abortus* (bovine type). Two blood cultures were negative for the brucella group after fifteen days.

Blood calcium was 10.1 mgm., inorganic phosphorus 2.45 mgm., and urea nitrogen 13.63 mgm., per 100 cc., of blood-serum. Blood calcium was also within normal limits on two other occasions, and the blood uric acid 3.9 mgm. per 100 cc. of blood on one occasion. Another spinal fluid, taken October 31, 1932, showed the Wassermann negative throughout, only 5 white cells, a very faint trace of globulin and albumin, a negative smear and culture, and a normal sugar content.

Sun-baths were being continued daily; the patient was given a course of neosalvarsan (4 doses) intravenously and three transfusions of blood, 300 cc. each, one being citrated and two whole blood.

During the latter portion of this period he was also given 130 mgm. of pyronin dye in capsule daily by mouth for a period of six days. (*Note:* Our use of pyronin was based upon an article by Forrest Huddleson under the title, *Differentiation of the Species of the Genus Brucella, Am. Jour. Pub. Health, 1931, xxi, no. 5*, in which it was stated that this dye should possess more therapeutic value against brucella than thionin or methyl-violet because it is effective in low dilutions against all three species and, if given sowly, may be injected intravenously in a 1 per cent solution (in monkeys).)

During the entire stage, heavy night-sweats had been noted rather frequently.

Fourth Stage: January 18 to June 17, 1933

On January 23, 1933, there was noted for the first time a swelling about 5.0 cm. in circumference and 1.5 cm. in height in the muscle at the level of the 11th dorsal vertebra, about 3.0 cm. to the right of the spinous process; there was no redness or local inflammation and but slight tenderness. While palpating the mass, with the other hand sliding with pressure from the right sacral region upward, the contents of the swelling were increased in volume. Aspiration showed a thick, creamy, odorless pus which was sent for smear, culture and

animal inoculation. Over a period of the next two months six aspirations were made in this area, with removal each time of varying amounts of the same type of pus, occasionally blood-streaked. Lipiodol was injected to show the origin of the pus which we felt came from bone-involvement somewhere. At subsequent aspirations the removal of the pus was followed by injection of 2 per cent pyronin dye in sufficient amount to distend the tract, the needle puncture then being sealed and the pyronin left *in situ*.

On February 14, 1933, there was noted some induration about the lymph nodes in the left inguinal region, and there was a tender area deep in the muscle just to the left of the 3rd and 4th lumbar vertebrae. This induration remained largely unchanged or increased very slightly for more than a month. The latter part of March the muscles in the upper part of the left thigh, anterior, internal surface, became indurated and definitely swollen, with, however, but slight tenderness and no redness. On April 1, 1933, the findings here indicated the need for aspiration, and 150 cc. of pus were withdrawn, lipiodol injected, and a radiograph made, showing the opaque material passing up to the level of the sacrum. During the ensuing month the left inguinal abscess was aspirated on three occasions, 192 cc. of pus being obtained on one occasion; on the second occasion 100 cc. of lipiodol were injected and left in the tract following the taking of a radiogram; after the third aspiration 100 cc. of 2 per cent pyronin dye were injected and left, and this was repeated on one subsequent occasion. Later the dorsal abscess showed some discharge through the old puncture opening, and there seemed to be a sinus leading from the upper part of the left ilium to the opening at the level of the 11th dorsal spine; pressure along this area produced a slight discharge.

The cough had continued severe during all this stage, with the daily expectoration of 30 to 40 cc. of a clear, colorless mucoid material, but it practically disappeared about May 1, 1933. The patient now had an excellent appetite and was gaining weight. Blood-pressure continued normal. There never appeared to be any reaction from the pyronin dye. On May 16, 1933, an intracutaneous test was done with antiabortus goat-serum with negative result, and the patient was given 15 cc. of the serum intravenously. This was repeated, May 22, 1933. (*Note:* The antiabortus goat-serum, with instructions for its use, was very kindly furnished us by Drs. William Wherry and Alfred E. O'Neil of the Cincinnati General Hospital, Cincinnati, Ohio, the serum having been developed there. Dr. Wherry announced its initial use in an address to the American College of Physicians at Montreal in 1933.)

The last aspiration of the psoas abscess was on May 18, 1933, following which 60 cc. of 2 per cent pyronin dye were injected.

Roentgenographic examination: February 24, 1933, following the lipiodol injection of the abscess in the dorsal region, showed the opaque medium in the soft tissues posteriorly to the spine (figure 3) and extending from the level of

the upper border of the 1st lumbar to the lower border of the 3rd lumbar, with a narrow tract extending inferiorly to a pocket at about the level of the 5th lumbar vertebra; there was no definite evidence of bone destruction at this time. A roentgenogram was made, April 10, 1933, following lipiodol injection of the left psoas abscess. The opaque medium passed as high as the crest of the ilium and downward to the upper portion of the left thigh but there was no apparent bony connection and no demonstrable areas of necrosis in the lumbar spine or pelvis (figure 4). Radiograms, made May 26 and June 16, 1933, indicated no particular change.

The urine continued for the most part negative, but occasionally there were white cells and single-plus albumin. Cultures of the urine on various media during December, 1932, and January, 1933, had been negative for brucella. Radiograms of the chest revealed no abnormalities of the heart and lungs, and the sputum had been negative for tubercle bacilli on several occasions, examination having been made because of the persistent cough and expectoration. A culture of the sputum gave nonhaemolytic streptococci and staphylococci.

The blood picture continued about as before with a mild secondary anaemia, the white count ranging generally between 6,000 and 9,000, with occasional higher counts, once to 16,000 on May 1st; the polymorphonuclear count was not significant.

Sedimentation test of the blood on February 7, 1933, was 14 per cent at 60 minutes; the blood-sugar was 94.3 mgm. per 100 cc. of blood. Icterus index was normal. Agglutinations for *Brucella abortus* continued positive at 1–320. Cultures of the blood which had been taken, January 4, 1933, and which had been carried through on various media, gave no growth and two guinea pigs inoculated intraperitoneally with blood were negative for gross lesions of any kind after six weeks; complement-fixation tests in one guinea pig and agglutination tests of the serum in both guinea pigs were negative. A blood specimen, taken May 12, 1933, gave complete fixation of complement in amounts of 0.15, 0.10, 0.05 and 0.002 in the presence of *Brucella abortus* (bovine) antigens. A culture of the spinal fluid, which had been carried from January 4, 1933 to March 27, 1933, was reported as negative.

Pus from the dorsal abscess on January 23, 1933, showed no acid-fast organisms on smear; gram stain and methylene-blue revealed no organisms; a fresh wet preparation was negative for amoebae and fungi; hydroxide preparation negative for fungi; no granules could be found either grossly or microscopically. Many cultures of the pus were made on various media and incubated at varying temperatures and CO_2 tension, none developing any growth grossly or microscopically. Four guinea pigs, injected with the pus subcutaneously in the left thigh, were killed and autopsied at varying periods from 19 to 56 days; one had a cyst at the point of inoculation; the others no lesion; no gross lesions were found anywhere at necropsy. Cultures made from their spleens in various

media were negative. The heart's blood of four contained no agglutinins for brucella; and the heart's blood of two no complement-fixing bodies for brucella. Pus taken from the same abscess, March 14, 1933, gave no growth on culture.

A study of pus from the abscess in the left inguinal region was negative throughout, and cultures on various media gave no growth in 48 hours,—this on three occasions. A final report regarding the various specimens of pus obtained in this case by Major H. R. Livesay, M.C., who was doing the special laboratory work states: "All specimens to date have shown no lesions in autopsied animals—guinea pigs and rabbits. Cultures have all been negative for brucella. One streptothrix or an actinomycoses isolated on culture."

The temperature during this stage had been irregularly elevated since the latter part of January, 1933, and for the three ensuing months, from 99° to 101° F. in the afternoon but with a few indefinite undulations of higher and lower temperature. Subsequent to April 22, 1933, the temperature remained normal almost continuously with only an occasional variation for a day or two when it might be as low as 97° or as high as 99.4°.

The pulse-rate had been more or less in proportion to the temperature, except that, as the illness progressed well into the second year, the pulse became more labile and remained a bit rapid, 80 to 108, even with a temperature not exceeding 99°F. During February, 1933, pyronin was given by mouth for six days, 200 mgm. daily. In March, 1933, four injections of salvarsan were given intravenously.

On April 19, 1933, a plaster body-cast was applied; this was cut as soon as it hardened and a posterior plaster trough made; from this date the patient was kept in a plaster trough continuously for eight months. Because of the finding of possible actinomycoses in one specimen of pus, he was given a course of potassium iodide during March and April, 1933, running the dose up to 275 grains daily and then discontinuing it; there was no apparent benefit of any kind following this treatment. On June 2, 1933, there was still slight drainage of pus from the abscess in the back and considerable drainage from the psoas abscess. In the early part of June, sun-baths, which had been discontinued for a time, were again started.

Fifth Stage: June 18, 1933 to May 1, 1934

From June 16, 1933 to August 16, 1933, the patient, on seven occasions, passed several small stones in the urine, which proved to be calcium. Blood calcium on June 25th was 10.3 mgm. per 100 cc. of blood. A radiograph of the abdomen revealed no stones in either kidney or ureter. The patient's appetite and general condition were excellent. By July, 1933, the pain in the lumbar region had practically disappeared; the temperature was normal; there was no cough; the blood-pressure was normal; and the patient was still getting sun-baths. A radiograph, July 12, 1933, showed evidence of bone regeneration

in the lumbosacral region; another, August 7, no further change; but one, August 31, showed a definite bony bridging of the lumbosacral joint (figure 5), and on one of September 8, 1933, this bridging was more marked and of greater density. Radiograms at monthly intervals later demonstrated only increased density of the bony bridging, with deposition of lime salts in the lumbar spine and pelvis. There was a considerable gain in weight, so that by February, 1934, it was again 190 lbs., stripped. Convalescence continued very satisfactorily; but, about November 25, 1933, the patient again complained of some excess of perspiration, especially about the neck and upper chest, and of some cough. A portion of detoxified brucella vaccine, which had been obtained for another patient, was administered with relief of these symptoms. (*Note:* We are also indebted to Drs. William Wherry and Alfred E. O'Neil of the Cincinnati General Hospital for the detoxified brucella vaccine used in this and another case of melitensis infection.)

On December 1, 1933, gradual elevation of the head of the bed was started, but the use of the plaster trough was continued. On December 13, 1933, the blood-pressure for the first time showed a definite rise, going to 195 systolic and 110 diastolic mm. Hg. The patient had been eating excessively and drinking very large amounts of fluids. Dietary correction led to reduction of the blood-pressure within one week to 142 systolic and 92 diastolic. On December 15, 1933, he was allowed to sit up in a chair for a few minutes with a body brace. The brucella-vaccine treatment of 10 doses was completed, December 24, without reaction, the last dose being 0.8 cc. The pulse was still inclined to be a bit rapid, but the quality was good. General physical condition was good, and patient feeling excellently. The perspiration and cough had ceased after the second injection of the vaccine. Blood-pressure returned, January 2, 1934, to 128 systolic and 80 diastolic. From this date activity was gradually increased, and he was soon up and about the ward. He left the hospital, February 15, 1934, on sick-leave with instructions to continue to wear the body-brace. Seen one month later, he had made a steady gain in strength, and had no cough, perspiration or temperature. Weight 190 pounds, stripped. Pulse 80 to 100. Physical examination negative except for some stiffness in the lumbosacral region. Blood pressure, 138 systolic and 85 diastolic mm. Hg. The blood picture and urine were normal. An electrocardiographic tracing on March 19, 1934, showed a slight sinus tachycardia with moderate left axis deviation and slight slurring of the QRS in two leads. During this period of convalescence the white blood count and differential had remained within practically normal limits. Because of the several stones passed in the urine, the blood-calcium was taken on several occasions during this stage and remained within normal limits. The urea nitrogen and sugar content of the blood were also normal on several occasions. The agglutination for brucella

remained positive, 1–320, on September 14, 1933, and 1–160 on October 7, 1933, and November 6, 1933; on January 26, 1934, it was positive 1–80.

On May 1, 1934, the patient was seen again. He was walking 5 to 6 miles daily with but slight fatigue. Appetite excellent, so that he had to control his food and fluid intake. Weight 185 pounds, stripped. Blood pressure 138 systolic and 92 diastolic mm. Hg. Physical examination negative, except for some stiffness in the lower lumbar region, the ichthyosis and the slight lymphoedema of the right leg which had been present since an operation in 1910. Blood agglutination for brucella positive, 1–80. Radiograph of lumbar spine and pelvis showed practically same picture in the lumbosacral joint as recently previous plates. A *K.U.B.* was negative for any stones in the genitourinary tract. Urine negative. Urine culture negative. Blood picture normal (red cells 4,980,000; white cells 7,500; haemoglobin 80 per cent; polymorphonuclears 65 per cent). Blood calcium 12.5 mgm. per 100 cc. of blood. Blood urea and sugar normal.

The body-brace was shortened to a corset-like support for the lumbar spine and pelvis, and the patient was instructed to wear this for another four months. A check was to be kept on blood-calcium at intervals.

DISCUSSION

The question in our case is the accuracy of the diagnosis, that is, with no positive cultures obtained from any source, is a definite diagnosis of brucella infection justified on the basis of the history, clinical course, positive agglutinations and the apparent elimination by laboratory study of other probable or possible aetiological factors?

Of the cases cited in the American literature, the 5 infections of the meninges with brucella gave a positive culture of the spinal fluid in all, while the one case of bone infection gave a positive culture from the pus, the blood being negative.

Of the 3 acceptable cases of meningeal infection cited in the foreign literature, two gave a positive culture from the spinal fluid and one was negative; of the 8 acceptable cases of bone involvement only one gave a positive culture, this being in the blood; yet three of the 8 negative cases are considered in this literature as classical examples of brucella infection of the bone,—Lassen (14), Jensen (15), and Botreau, Roussel & Huord (17),—and all of these have many points of similarity to our case.

While it cannot be said there is any specific agglutination titre which is diagnostic, a titre of 1–80 is generally so accepted; the titres are generally not so high as in our case except in the presence of an active infec-

tion, those due only to antibodies from the use of infected milk being in the low range, at least below 1–100.

Negative cultures of the blood, pus, urine, etc., may be explained, as they are by many writers, as being due to the age or chronicity of the condition, positive cultures being obtained usually in the early stages.

It would seem that tuberculosis may be eliminated as a causative factor in our case by the negative history of tuberculosis, the absence of tuberculous lesions elsewhere in the body, the numerous negative smears and cultures, the radiographic appearance of the bone lesion which is entirely different from that seen in tuberculosis of the bone (see figures 1, 2 & 5), that is, too little of a destructive and too much of a regenerative process, and more specifically by the numerous negative animal inoculations.

Typhoid fever is eliminated by the numerous negative cultures of the urine, blood, pus and stools, by the clinical course, and, inferentially at least, because of the fact that the patient had previously had several courses of typhoid vaccine.

Actinomycosis was suspected after the obtaining of one positive culture of the many made from pus from the abscesses; but, as the examination of many specimens of pus revealed no granules or organisms after various laboratory procedures, the one positive culture of a suspicious organism is not diagnostic; further, in actinomycosis we would expect multiple localizations, more surrounding infiltration of the involved areas and only a small quantity of pus. Also, there was no improvement in our case after the administration of large doses of potassium iodide.

Other infectious agents do not appear to deserve consideration because again of the numerous negative cultures from the various sources, negative animal inoculations, the character of the white blood count and the clinical course.

Although antisyphilitic treatment in the form of mixed treatment and arsphenamine was given on several occasions during the course of the disease, syphilis was certainly not a factor, as evidenced by the repeated negative serological findings in the blood and spinal fluid, even if the negative history of infection is not credited as being of value.

In favor of brucella as the aetiological factor are the undulant and irregular type of fever, the mild secondary anaemia, the general low white blood count with low polymorphonuclears, the marked sweating, the loss of weight, the orchitis, cough with abundant mucopurulent

expectoration, the long duration of the disease, the positive agglutinations and the apparent elimination of other infectious agents.

The late development of bone involvement as a complication of brucella infection, mentioned by Roger (8), was exemplified in our case; at least we were unable to demonstrate any changes in the roentgenogram until twelve months after the beginning of the patient's illness, and abscess-formation did not take place until three months after the first bone changes were noted.

The prognosis, it appears from the literature, is almost universally good in these cases.

Our treatment probably left something to be desired as a formulated plan carried out to its completion. The pyronin dye seemed to have a definitely beneficial effect when injected into the abscess tracts and the goat's serum and antiabortus vaccine were also markedly effective in the relief of subjective and objective symptoms. The patient himself noted and remarked upon the relief which he experienced from the above mentioned remedies. Intravenous injections of mercurochrome, arsphenamine, and antimony and potassium tartrate have been previously tried by us in cases of brucella infection with no obvious benefit.

CONCLUSIONS

1. The available literature concerning meningeal and bone involvement in brucella infections in the human being is briefly reviewed.

2. A case is described of probable brucella infection (bovine type) with the complicating features of both spinal meningeal and bone (lumbosacral joint) involvement, with complete recovery after two years and three months.

3. It is held that a positive diagnosis may be made in such cases, notwithstanding negative cultures from the usual sources, by means of a practical consideration of the history, clinical course, agglutination reactions and the elimination by various laboratory procedures, including animal inoculation, of the other possible aetiological factors.

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BIBLIOGRAPHY

(1) Sanders, W. E.: Undulant fever meningitis (organism in spinal fluid), J. Iowa M. Soc., 1931, xxi, 510.

(2) Hansmann, G. H., and Schenken, J. R.: Melitensis meningo-encephalitis—mycotic aneurism due to Brucella melitensis, variety porcine, Am. J. Path., 1932, viii, 435.

(3) Kulowski, J., and Vinke, T. H.: Undulant (malta) fever spondylitis—report of a case, due to Brucella melitensis, bovine variety, surgically treated, Jour. Am. Med. Assoc., 1932, xcix, 1656.

(4) DeSage, Pellerin and Vinerta: A case of meningitis melitensis, contribution to the study of malta fever meningitis, Los Progresos de la Clinica, 1926, xxxiv, 452.

(5) Bingel, A., and Jacobsthal, E.: Meningitis in Bang's infection, its clinical and bacteriologic-serologic picture, Klin. Wchnschr., 1933, xii, 1093.

(6) Rouslacroix, A.: Méningite et symptomes d'hypertension intracranienne consecutifs a une melitococcic; trépanation décompressive; guérison, Marseille Méd., 1925, lxii, 1814.

(7) LeMaire, G.: Méningite a melitocociques; altérations importantes de liquide céphalo-rachidien; hyperglycorachie; guérison, Bull. & Mém. Soc. Méd. Hôp. Paris, 3 s., 1924, xlviii, 1636.

(8) Roger, H.: La spondylite mélitocociques, Presse Méd., 1926, lix, 929.

(9) Brun, G., and Brunet, E.: Sur une ostéite suppurée à micrococcus melitensis chez un sujet convalescent de fiévre mediterraneenne, Bull. & Mém. Soc. Nat. Chir., 1924, l, 425.

(10) Weil, S.: Skeletterkrankung bei Febris undulans Bang, Zentralbl. Chir., 1930, p. 1269.

(11) Cuatrecasas, J., and Gascia Tornel, L.: Un caso probable die fiebre de malta con fracturas espontaneas, Arch. Med. Cir. y. Exp. Madrid, 1928, xxviii, 669.

(12) Casaneuve, H. J.: Ostéo-périostite post-melitococcique, Bull. Soc. Path. Exot., Paris, 1913, vi, 668.

(13) Clerici, C.: Sulla spondilite da febbre ondulante, Gior. Clin. Med., 1932, xiii, 2.

(14) Lassen, H. K.: Et Tilfaelde af Spondylitis paa Basis af Infektion med. Bac. Abortus (Bang), Hospitalstid., 1930, no. 3.

(15) Jensen, J. P.: Spondylitis e bacillo abortus (Bang), Ibid., June 14, 1928, p. 637.

(16) Redell, G.: Spondylitis als Komplikation von Febris undulans Bang, Acta chir. Scandinav., 1931–1932, lxix, 87.

(17) Botreau, Roussel and Huord: Melitococcic spondylitis and sacro-iliac arthritis with bilateral abscesses of the buttocks resembling cold abscesses, Bull. & Mem. Soc. Nat. Chir., 1931, lvii, 1561.

(18) Brault, J.: Malta fever with osteitis of the femur, left tibia and of the bones of the cranium, Gaz. Hôp., 1910, lxxxiii, 1335.

TUBERCULOSIS OF THE SHAFTS OF LONG BONES

A Clinical and Roentgenological Study with Report of 8 Cases

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In a review of the bone cases treated at Glen Lake Sanatorium we find that we have 8 cases in which a tuberculous lesion was limited strictly to the shafts of long bones.

Case Reports

1: P. B., white, female, aged 24 on admission to the Sanatorium, August 27, 1931, for treatment of far-advanced bilateral pulmonary tuberculosis. Her course in the Sanatorium was entirely satisfactory from the standpoint of her pulmonary lesions which were treated by collapse therapy. In June, 1932, the patient received a slight injury to the dorsal side of her left forearm by striking it against a bedside stand. In September she became conscious of tenderness in that region. This was accompanied by swelling, redness and heat. An X-ray film, September 21, 1932, showed a normal condition of the bones of both wrists and the distal halves of the forearms. During the next three months the local findings became more pronounced. A film, December 16, 1932, showed a rounded defect, about 1 cm. in diameter, in the distal end of the ulna with a small amount of periosteal new bone on the medial surface of the ulna at the level of the defect. There was soft tissue swelling over the ulna proximal to the defect (figure 1a). On December 23, 1932, the soft-tissue mass was aspirated and about 30 cc. of purulent material obtained. The aspirated material showed no organisms on stained smear, but a guinea pig inoculated with the material developed tuberculosis. Following the aspiration a sinus tract developed which ultimately closed in July, 1933. The swelling subsided entirely, and motion of the wrist is perfectly free, with no tenderness on pressure in any part. Subsequent X-ray examinations showed a gradual replacement of the defect in the ulna by normal bone structure, and the periosteal new bone was entirely absorbed (figure 1b).

2: B. E., white, male, aged 75 on admission to the Sanatorium, November 7, 1932, for the treatment of far-advanced bilateral pulmonary tuberculosis.

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FIG. 1a FIG. 1b FIG. 2a FIG. 2b

FIG. 3 FIG. 4 FIG. 5 FIG. 6

FIG. 1a. X-ray of left wrist, case 1, December, 1932. Shows bone destruction in distal end of ulna

FIG. 1b. X-ray of left wrist, case 1, December, 1933. Shows new bone-formation

FIG. 2a. X-ray left tibia, case 2, June, 1933. Shows multilocular area of destruction

FIG. 2b. Photomicrograph showing tuberculous granulation tissue lining cavity in bone, case 2

FIG. 3. X-ray right humerus, case 3; shows multilocular area of destruction with periosteal new bone on medial side of shaft

FIG. 4. X-ray right humerus, case 5, February, 1933; shows extensive destruction and new bone-formation

FIG. 5. X-ray left ankle, case 6; shows area of bone destruction in tibia with marginal sclerosis due to secondary infection

FIG. 6. X-ray left tibia and fibula, case 8, showing area of bone destruction with beginning cortical erosion

His pulmonary condition improved slightly under routine sanatorium care. On June 30, 1933, the patient called attention to a "sore spot" on his left leg. He stated that this tender area had been present just distal to the knee joint for three or four months. Lately there had been a dull pain in this region day and night. Examination revealed a tender area just below the tibial tubercle, about 4 x 6 cm. in size, which was slightly swollen and hot. X-ray films made July 3, 1933, showed a loculated area of bone destruction in the proximal third of the left tibia. This area was 4.5 x 2.5 cm. There was a small amount of periosteal new bone along the lateral and anterior margins of the bone at the level of the involvement (figure 2a). A modified Orr operation was performed, July 11, 1933. About 0.5 oz. of pus was obtained. The cavity in the bone was filled with pus and necrotic bone and was lined with tuberculous granulation tissue (figure 2b). A guinea pig inoculated with the pus developed tuberculosis and the tissue showed tubercle-formation. There was complete healing of the skin wound within three months, but apparently no attempt at filling in of the operative defect in the tibia. The patient has no symptoms referable to the affected part.

3: J. S., white, male, aged 27 on admission to the Sanatorium, February 1, 1933, for the treatment of tuberculosis of the 8th and 9th dorsal vertebrae, and the right sacroiliac joint. Under routine sanatorium care and heliotherapy the patient's condition showed marked improvement. About the middle of August, 1933, the patient began to complain of pain in the right upper arm which radiated to the fingers and shoulder. Examination, October 5, 1933, revealed, for the first time, a point of tenderness on the humerus at the level of the deltoid insertion. There was no demonstrable swelling, but there was local heat. X-ray films made of the shoulder and humerus, October 6, 1933, showed a loculated defect, 4.5 x 2 cm., in the shaft of the humerus at the level of the junction of the proximal and middle thirds. This was primarily in the medulla but involved a small amount of the cortex on the medial side. Over the involved cortex there was a moderate amount of periosteal new bone (figure 3). A modified Orr operation, October 9, 1933, liberated about an ounce of pus. The appearance of the lesion at operation was identical with that of the preceding case. Acid-fast organisms were obtained on culture of the exudate. The wound healed within three months. There has been moderate new bone-formation in the operative defect in the shaft of the bone. There are now no symptoms referable to the lesion.

4: U. S., white, male, aged 27, admitted to the Sanatorium December 29, 1930, for the treatment of far-advanced pulmonary tuberculosis, fistula-in-ano, and tuberculous enteritis. His progress has been satisfactory under sanatorium care. Early in January, 1933, the patient struck his left shin

against an X-ray table. This bothered him for only a few days. A few weeks later, however, a swelling appeared which was tender on pressure. On March 1, 1933, examination revealed a red, swollen area just below the left tibial tubercle, which was definitely tender on pressure and warmer than the surrounding skin. X-ray examination showed only slight soft-tissue swelling over the area in question with no evidence of bone involvement. During the next month the symptoms became more severe. On April 4, 1933, a modified Orr procedure was carried out in spite of the fact that the X-ray at that time was still negative. Pus, granulation tissue and necrotic bone were removed. The tissue removed at operation showed tubercle-formation. Emulsified granulation tissue was inoculated into a guinea pig which developed tuberculosis. The wound was entirely healed in two months. Normal bone structure is filling in the operative defect.

5: K. O'B., white, female, aged 4 months on admission to the Sanatorium, August 14, 1931, because of exposure to tuberculosis at home. In October, 1931, the patient developed primary pulmonary tuberculosis. On a routine film of the chest, February 23, 1933, a lesion in the right humerus was noted (figure 4). This lesion consisted of numerous areas of destruction in the proximal half of the shaft but not involving the center for the head. Both the medulla and the cortex were involved. There was a marked amount of periosteal new bone. Examination of the child revealed no evidence of the underlying changes. The lesion gradually improved by a process of new bone-formation in the shaft and resorption of the periosteal new bone. At no time did the patient have symptoms.

6: O. S., white, male, aged 20, admitted to Glen Lake Sanatorium, May 29, 1928, for the treatment of tuberculosis of the lower end of the left tibia. The patient had been treated from May to November 1927 for primary pulmonary tuberculosis involving the left hilum lymph nodes. Some time in March, 1928, he noticed soreness and swelling about the left ankle, and two months later the swelling over the external malleolus ruptured, discharging yellow watery pus. On admission, examination revealed diffuse swelling of the lower leg and ankle, with a dark red indurated area, about 3 cm. in diameter, over the external malleolus. In the centre of this there were two small draining sinuses. X-ray films made of the ankle joint showed a small, rounded area of destruction within the distal end of the tibia, about 1.5 cm. from the joint margin. There was a narrow zone of sclerosis about the defect (figure 5). Material from the sinuses was injected into a guinea pig on three occasions, one week apart, and the animal showed tuberculosis when killed September 14, 1928.

Under conservative therapy, consisting of bed rest and heliotherapy, the

lesion completely filled in with normal bone structure. The sinuses healed after 8 months of treatment.

7: H. S., white, male, aged 22, admitted to Sanatorium, June 18, 1925, for pulmonary tuberculosis and tuberculosis of lower end of left humerus and upper end of right tibia. In March, 1925, the patient noticed soreness and swelling just above the left elbow. A sinus opened spontaneously in this region about April 15, 1925, and continued to drain. The upper anterior portion of the tibia became sore to the touch about June 15, 1925. Examination on admission revealed a flexion deformity of the elbow, (90°) with two draining sinuses, about 2 cm. above the internal epicondyle. No definite tenderness was noted over the lower humerus. There was inability to flex the right knee. A circumscribed abscess, accompanied by local heat, pain, and fluctuation, was present just below and lateral to the tibial tubercle. X-ray films made of the left elbow and humerus, June 23, 1925, showed a rounded area of bone destruction in the lower third of the humerus with periosteal new bone-formation on the medial and posterior aspects, just above the medial epicondyle. Films made of the right knee joint on the same date showed a large area of bone destruction, 7 x 3.5 cm., in the upper third of the tibia with periosteal new bone on the lateral side of the tibia. There was a similar area of destruction, 1 x 1.5 cm., in the proximal third of the fibula. In August, three guinea pigs were inoculated with material obtained from the abscess below the right knee, and all developed tuberculosis. Subsequent films of the knee joint are not available. X-ray examination of the right humerus was again done, December 31, 1925, showing an increase in the size of the defect, with marked sclerosis and new bone-formation. There was at this time a sinus tract through the cortex, 2 cm. above the epicondyle. The patient was treated with bed-rest and heliotherapy during residence and discharged, January 10, 1926, unimproved, against advice, and died June 5, 1926, of pulmonary tuberculosis.

8: A. H., white, male, aged 17, admitted to Sanatorium, June 20, 1932, for treatment of moderately advanced pulmonary tuberculosis and tuberculous cervical adenitis. His progress was satisfactory under routine care and he was started on graduated exercise, July 18, 1933, advancing to 3½ hours. On February 5, 1934, he complained of pain in his left leg, stating that this had been present for about a week when he was walking, but that during the past two or three days it had been aching when at rest. Physical examination revealed definite tenderness and local heat over the anterior surface of the left tibia at about its middle third. X-ray examination showed an oval area of bone destruction in the posterolateral portion of the tibia at the junction of the lower and middle thirds. On February 15, the discomfort had increased.

Tenderness and local heat were more marked and X-ray films at this time revealed an increase in bone destruction, with beginning involvement of the inner side of the cortex. There was no elevation of body temperature or other general symptoms of infection (figure 6). Surgical intervention revealed a mass of granulation tissue adjacent to a beginning excavation of the inner side of the cortex. This granulation tissue was curetted away after removal of the overlying cortex. No periosteal new bone was noted at operation. A guinea pig inoculated with the material removed at operation developed tuberculosis. The wound healed rapidly and the patient was again on 3½ hours exercise six weeks after operation.

CLINICAL DIAGNOSIS

The clinical picture presented by this type of lesion is that of a low-grade bone abscess arising in the cancellous portion of long bones. The symptoms in adults, as shown by the case reports, are quite constant. There is at first an indefinite area which is tender on pressure and painful with active motion of the part. This is followed by definite throbbing pain during rest. Eventually soft tissue swelling and local heat make their appearance. If allowed to go on, the bone abscess perforates the cortex and soft tissues, resulting in sinus-formation.

At no time do general symptoms of toxaemia occur. The white blood count and body temperature remain within the range of normal.

In all our cases there existed at the time of appearance of these bone lesions, a definite pulmonary tuberculosis. The one child in the series showed a concomitant development of a primary pulmonary lesion and the bone lesion; and they both progressed and subsided together.

Clinically it is extremely difficult to differentiate this type of tuberculous bone lesion from syphilis, pyogenic osteomyelitis, and Brodie's abscess, since any one of these latter may occur in tuberculous individuals. The symptoms and physical signs of all are fundamentally the same, differing, however, in severity.

The usual picture in pyogenic osteomyelitis is that of an acute infection occurring in childhood, with severe systemic and local symptoms and signs. Low-grade, slowly developing pyogenic abscesses, however, may simulate the picture of tuberculosis, and, as with some cases of syphilis, can only be proved by laboratory and operative procedures. Brodie's abscess is a chronic pyogenic abscess, nontuberculous in origin, occurring in the spongy portion of long bones. Its clinical picture is similar to tuberculosis in that it produces the same signs and symptoms and may

go on to perforation and sinus formation. Here again laboratory, X-ray, and operative aids must frequently be used for differentiation.

Syphilis of the shaft of long bones is fundamentally a periosteal reaction, causing gross thickening and change in shape of bone. The tenderness is only moderate and local elevation of temperature is not noted. In syphilis one does not see sinus-formation and the blood Wassermann reaction is positive.

In considering the three lesions mentioned a negative intracutaneous tuberculin test is, of course, a valuable aid in ruling out tuberculosis. Smears, cultures and guinea-pig inoculations of exudates from the lesion will assist in establishing the aetiology.

X-RAY DIAGNOSIS

From an X-ray standpoint the lesions are noted first in the cancellous portion of the bone. They appear as rounded areas of decreased density. In some of our cases this defect in the bone was loculated, giving the impression that two or more foci had become confluent. The areas of decreased density appear clean-cut, but not in the sense that there is a limiting region of bone sclerosis. Neither do they fade into normal bone structure. Rather, there is simply an abrupt transition about their margins from apparently normal trabeculated bone to the defects in which the bone structure cannot be seen. If sinuses develop, new bone-formation may occur in the defect due to secondary infection.

As the process extends to the cortex, it wipes out the structures in its path. On the X-ray film this has the appearance of erosion from within. Finally, when the periosteum is approached, it reacts characteristically by laying down new bone.

In differential diagnosis, the conditions which cause confusion clinically must also be considered roentgenologically. In addition, it may be necessary at times to rule out such rare bone infections as blastomycosis and coccidiodal granuloma.

In all our cases we could exclude pyogenic osteomyelitis because of the chronicity of the lesions we are describing. Also, the type and amount of new bone-formation was not that usually seen in orthodox osteomyelitis. Brodie's abscess is easily excluded by the absence of a localized, fusiform increase in density and thickening of the cortex about the defect. Syphilis is usually a roentgenological possibility in obscure bone lesions. However, in syphilis, new bone-formation usually plays a more prominent part than it did in this series of cases. In the final analysis, the Wasser-

mann reaction and, if necessary, a therapeutic test must be the deciding factors if there is question of a syphilitic aetiology from an X-ray standpoint.

TREATMENT

From the standpoint of treatment we can only say that among our patients those who were operated upon were greatly benefited. This statement does not take into consideration the child (case 5) in whom the condition was asymptomatic. Surgical treatment reduces the period of morbidity and reduces to a minimum the possibilities of complications. Therefore this type of treatment is more satisfactory from all points of view than is conservative management.

DISCUSSION

Tuberculosis of the shafts of long bones is relatively rare. This is forcefully brought out by the fact that 8 cases represent the total number encountered in a series of 4,896 admissions to the Sanatorium. Of this total number of admissions, 275 patients were suffering from bone and joint tuberculosis, with or without pulmonary manifestations. Thus, in the total number of bone and joint tuberculosis cases in the institution 2.9 per cent have shown this type.

We see no need for the several schemata of classification which have been suggested by various authors. We believe that the numerous types described represent different phases of tissue reaction and not separate clinical entities. In our series of cases tuberculous involvement of cancellous bone resulted in bone destruction. On the other hand, when the lesion extended to cortical bone it was followed by bone proliferation. Thus, the so-called atrophic, hypertrophic and cystic types are explained very simply. These observations are borne out by the operative and X-ray findings. The only classification that seems of value is one which is based on location of the lesion.

SUMMARY AND CONCLUSIONS

1. Eight cases of tuberculosis of shafts of long bones are presented.
2. Tuberculosis of the shafts of long bones is quite rare. In our series it amounted to 2.9 per cent of all cases of bone and joint tuberculosis.
3. The differential diagnosis of shaft lesions of obscure aetiology should always include tuberculosis, syphilis and pyogenic osteomyelitis.
4. We believe that tuberculosis of the shafts of long bones is primarily

destructive in the cancellous portion, but that it becomes proliferative when the periosteum is approached.

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BIBLIOGRAPHY

BROMER, R. S., AND DOWNS, E. E.: Tuberculosis of the diaphysis, Am. J. Roentgenol. & Rad. Therapy, 1933, xxix, 617.

HENDERSON, M. S., AND SIMON, H. E.: Brodie's abscess, Arch. Surg., 1924, ix, 504.

LOVETT, R. W., AND WOLBACH, S. B.: Roentgenographic appearance, diagnosis and pathology of some obscure cases of bone lesions, Surg. Gynec. & Obst., 1920, xxxi, 111.

WILENSKY, A. O.: Chronic abscess of bone, Am. Jour. Surg., 1928, v, 455.

CONTROLLING FACTORS IN THE PRODUCTION OF CAVITIES AND PSEUDOCAVITIES OF THE LUNG[1]

EDGAR MAYER

The tuberculous cavity is one of the paradoxes of nature in that it destroys as it heals; in it a remarkable healing process is turned into its most effective disseminator. This turn of events seems all the more unfortunate because, when the systemic signs of tuberculous infection seem to have been overcome, and the lung is the seat of an isolated process, this last stronghold must be overcome at the sacrifice of this and perhaps of life.

AETIOLOGY

We may accept it as a matter of course that the only aetiological agent in the production of the tuberculous cavity is the Koch bacillus; even in this day some workers still contend that cavity-formation depends upon toxic effects of mixed-infection organisms in tissues in which the destruction has been initiated by tubercle bacilli; but overwhelming evidence available to-day indicates that the tubercle bacillus can and does accomplish by itself all the tissue destruction that goes on in pulmonary cavities of any size. We must consider, however, as forming a part of the aetiology those other factors which determine the character and evolution of the infection. In this sense we may speak of the various phases and forms of tuberculosis which play a rôle in cavity-formation as a part of the aetiological factor. Indeed, in speaking in modern terms of any infection—but particularly of tuberculosis—we are accustomed to include in the infectious complex the rôle played by the quantitative and qualitative factors of the infectious agent, as well as the rôle played by the response of the host.

It would carry us too far afield to enlarge upon the diverse conceptions held regarding the problem-complex of immunity in tuberculous infections in man; but we must refer to the question here to the extent to which it is believed that immunity factors, shaping the course of tuber-

[1] Read at a stated meeting of the New York Academy of Medicine, New York City, March 1, 1934.

culosis, determine whether or not a cavity-producing type of tuberculosis shall arise, and perhaps also determine important characteristics of such cavities as are produced. Of course, in the final analysis, we know scarcely anything definite about the concrete factors upon which the defense of the body in tuberculosis depends. We know that what we have come to call "allergy" is one of its important manifestations. *Allergy*, in tuberculosis, is a much-used term familiar to us all, although its nature is in reality hardly known to any of us; we may accept that it represents a *hyperergic* reaction. Now it is generally agreed upon by the majority of workers that the cavity represents such an allergic reaction to the tuberculous invasion.

In continental literature we read quite a number of attempts to connect cavity-formation with various types or forms, phases or stages of tuberculosis; and there are some interesting though largely speculative attempts in this direction in our own literature. On the face of the available facts it would seem very reasonable to believe that cavities arising abruptly in association with more or less acute infiltration or caseopneumonic processes represent just such an allergic manifestation.

However, cavity-formation is a characteristic lesion of chronic pulmonary phthisis, in which it is also the chief source of dissemination of a process assumed to be predominantly productive and markedly chronic. If, therefore, we are not to abandon the concept of the allergic nature of the cavity-producing process, we must hold with Huebschmann (1) that essentially exudative or inflammatory events form the initial phase of formation of new foci in any stage or form of tuberculous processes, and that allergic manifestations are in the nature of an ever-recurring feature in the evolution of tuberculous disease in general, regardless of stage or form.

This concept is of considerable help when we attempt to explain certain characteristics of the cavity-producing process in some forms and types of pulmonary tuberculosis. We can visualize the course of events observed when a certain, well-defined type of cavity, which will be discussed later, makes its rapid appearance in an area of an acute exudative infiltration, to soon disappear just as rapidly as the infiltration is absorbed. It is perhaps descriptive of the event when, in terms of immunity, some workers speak of this type of cavity as the "secondary cavity," a term which refers to Ranke's second stage of tuberculosis, which is the stage of generalization of the process characterized by intense "allergic" reacting tendency. It is in line with this concept that the

lesions which break down to form such "secondary cavities" are believed to be haematogenous in origin. It is said that the cavity-producing reaction is exaggerated in this case, so that tissue is involved and frequently destroyed beyond that reached by the bacilli, and that this subsequent evacuation leaves a well cleaned cavity of punched-out aspect. It is also stated but, as yet, greatly to be questioned that, generally speaking, haematogenous lesions proceeding to chronic progression represent invasion by bacilli mild in amount or virulence, and that this explains the indolent nature of what is sometimes referred to as the "haematogenous cavity." It is true that such a cavity is occasionally seen to remain patent for many years without great danger to its bearer as far as extension of the process is concerned.

We must not lose sight of the fact that, logical and helpful as some of these concepts are, they must still await substantiation and further clarification of the many as yet unsolved phases of this entire problem complex.

PATHOGENESIS AND HEALING OF CAVITIES

The processes involved in the production of cavities also enter into their healing: and so the pathogenesis and the healing of cavities must be discussed together.

We must distinguish clearly between the rôles of two paramount factors which are closely interrelated and see how they mostly supplement, but also how at times they oppose each other. These two factors which we are about to discuss separately, as well as in their interrelation, are (1) the pathological process which underlies tissue destruction and repair and (2) the mechanical processes inherent in pulmonary dynamics which inflate and deflate the lung.

The making and unmaking of pulmonary cavities

The factors which play a rôle in the production are also operative in the obliteration of cavities in the lung. Two such factors must be recognized, namely (1) the pathological process of cavity-production and healing, and (2) the mechanics of pulmonary inflation and deflation. These factors work in such correlation that at times they aid, at other times they counteract, each other.

1: The pathological process of cavity production and healing: It is perhaps superfluous to enter upon the discussion of the pathological features of

tissue destruction; suffice it to point out that the process is not quite clarified as yet in many of its phases. We know that the bacillary toxins poison the tissues invaded. The cells of the local tissue structures as well as those of the tuberculous tissue products degenerate into that formless substance termed "cheese." Caseation is followed by liquefaction under the action of leucocytes supplying the ferment, and the tuberculous pus thus produced is then evacuated, leaving behind the tissue defect, the cavity. Caseation is however not necessarily followed by liquefaction and evacuation; frequently enough a caseated focus may undergo inspissation and calcific transformation, provided a healing tendency prevails. Thus healing with calcification is quite characteristic of the lesions of primary tuberculosis. The lesions of chronic pulmonary phthisis usually develop a solid capsule at the periphery, even before their centre begins to caseate. This capsule consists of an inside layer of cells of the specific tuberculous-tissue proliferation and an outside layer of connective-tissue fibres which separates the lesion from surrounding sound tissue. With regard to its morphological features the smallest tubercle differs little from the larger tubercular lesion. However, while a small focus even after caseation and discharge of its liquefied contents may be grown over by granulation tissue, evacuation of a larger focus must needs, of course, leave a tissue defect—the cavity. Available anatomical evidence would indicate that the largest tissue destruction which can be repaired without leaving an interruption of continuity, namely, by connective-tissue replacement, is such as would leave a cavity of about the size of a cherry, that is, about $\frac{3}{4}$ inch in diameter. Naturally, there will also be extensive connective-tissue proliferation about tissue defects of larger size, and fibrosis will always be proportionate to the extent of the lesion, but defects of more than about three-quarter-inch diameter can no longer be prevented by the natural reparative processes. At this point, however, another process, namely, cirrhotic shrinkage of the granulation tissue comes into play. While this process is a rather slow one, requiring at times years, it frequently accomplishes complete obliteration of large cavities.

It follows from the above that on the basis of anatomical evidence it is not possible to explain the disappearance of cavities, particularly not of such size as one frequently observes disappearing in clinical practice, without leaving a trace. Pathologists agree, with regard to the evidence, that it is not possible for a cavity of more than cherry-size to heal spontaneously without leaving a scar, which should be well visible

in the roentgen film. They also agree on the fact that pulmonary tissue once destroyed does not regenerate. There arises thus the problem of the spontaneous disappearance of cavities of greater than cherry-size.

A number of suggestions have been made in an attempt to circumvent this difficulty. Barat (2) conceived the idea that the ring-shaped shadow, the traceless spontaneous disappearance of which is to be explained, does not represent a real cavity but merely "*precavity demarcation*" about an exudative focus preceding its eventual excavation. This line of demarcation about an exudative focus would consist of the specific cellular elements, particularly lymphocytes and connective tissue. While the central exudative elements of the focus are rapidly absorbed as soon as a healing tendency in the lesion takes the upper hand, the productive ring about it may continue for some time further, to disappear later. It is conceivable that such a sequence of events would simulate the picture of cavity absorption, but there is as yet no pathological evidence to substantiate the assumption that this is what really takes place.

Another explanation, which ought at least to be considered in some instances, is that we are dealing here with an *interstitial dissecting process* which comes to a halt before real destruction ensues. This concept may be drawn on the analogy of similar sequestrating processes in the lungs due to other destructive infections but especially adapted to the particular mode of spread of tuberculous infections. Not infrequently destructive lesions in the lungs extend along the interstitial septa instead of contiguously, so that uninvolved sections of lung tissue are left in form of sequestra, lying within the circle of destruction which outlines the cavity to be. That the lymphatic route is the most favored mode of spread in tuberculous infections and that, in the lungs, the lymphatics run along the interstitial septa, needs no further discussion. It is conceivable that some of the ring- or oval-shaped shadows represent just such interstitial dissecting processes extending around several lung units by a wall of tuberculous tissue travelling with the lymphatics along the interstitial septa. It needs hardly any assertion that such processes are capable of much healing and absorption. In the literature we find frequent reference to residues of such processes under the name of "reticular lymphangitis." Indeed, the so-called healed and spontaneously disappearing "cavities" usually leave a network of fibrosis which corresponds exactly to what is frequently pictured in the literature as reticular lymphangitis.

2: The rôle of the mechanics of pulmonary inflation and deflation: That the cavity represents a mechanical problem has become a well-recognized fact by now. The treatment of cavities based on this concept has proved to be the most successful measure ever introduced in tuberculosis therapy. It is all the more surprising therefore that the rôle of pulmonary mechanics in the production and healing of cavities has not as yet been properly evaluated. An attempt will therefore be made in the following to review this subject in the light of more recent data.

To explain the apparent contradiction between clinical experience and pathological evidence, doubt has repeatedly been expressed in the literature as to the genuine cavity nature of roentgenographic cavity outlines, the traceless disappearance of which has been observed. Particularly, the suggestion has repeatedly been made that the outline of the cavity shown by the roentgen picture does not represent at all the extent of the actual tissue destruction present, the contention being that we are dealing here with exaggerated cavities due to mechanical distention of the tissue defect out of all proportion with the actual underlying tissue destruction present. The theory particularly favored is that obstruction of the tributary bronchus with valvular obstruction leads to hyperinflation of the cavity. The literature on this subject generally lacks appreciation of the real nature of the mechanical factors playing a rôle here. Yet it should appear that the questions which have been raised with regard to the mechanics of cavity formation may now be answered on the basis of newer data available on the mechanics of lung inflation and deflation.

For full appreciation of the rôle of pulmonary mechanics in cavity production and healing, knowledge of the *mechanical principles involved in pulmonary ventilation* is prerequisite. Much of this field has recently been restudied. Particularly its relationship to phthisiogenesis and phthisiotherapy has recently been the subject of discussion by Orsos (3), Loeschcke (4) and most recently by Parodi (5). Lack of space does not permit more than mere mention of some of the fundamentals necessary for the discussion of the particular phase in which we are interested here.

It is now a well established fact that the lung, even while at rest, but particularly during its movements, is under permanent tension pervading all of its parts, although unequally so. It is this tension to which Forlanini attributed the "traumatization of the lungs" which he sought to eliminate by artificial collapse. The phenomenal results obtained

with this therapy is the greatest possible proof of the correctness of the concept of Forlanini of constant lung "trauma," the effect of which can hardly be overestimated. Parodi (5), a pupil of Forlanini, demonstrated and set down the following three fundamental principles of pulmonary mechanics: (1) The "static tension" of the lungs due to gravity (weight) is greatest at the apices upon which the lungs are suspended within the airtight pleural space; (2) The "dynamic tension" of the lungs, which comes into play as the lung is being inflated under the force of thoracic traction in inspiration, is greatest in the upper narrowing cone of the lungs, where distensible lung tissue decreases in amount; and (3) both static and dynamic tensions are increased in any part of the lungs which is the site of lesions because the weight of such a lung section is increased while its distensibility is reduced.

From these principles we may suggest not only the predisposition of the upper parts of the lungs to incipient tuberculosis but also the tendency of tuberculous lesions in these pulmonic areas to progress to cavity formation and indeed to production of cavities frequently far in excess of the actual tissue destruction present. Furthermore, they afford also an explanation of the mechanical factors which favor tissue reparation and indeed the disappearance of the cavities produced.

The sequence of events may be outlined somewhat as follows: The prevailing high tension in the upper third of the lungs will favor implantation of infection here above all other lung areas. Lesions developing there will tend to progress, particularly if the patient is up and about. As the lesions extend and distensibility of the lung section involved decreases, tension continues to increase and may reach such proportions that under its force an artificial air-pocket is produced in the form of a *bleb* which may become localized within the lung itself, or under the pleura. These would then be the "pseudocavities" due to interstitial or subpleural blebs, repeatedly referred to in the literature and even observed postmortem by Huebschmann (6). It is a matter of course that such air-blebs sucked in to fill space will tend to localize where tension is greatest, namely, in or about the infiltrated areas. It also needs hardly any explanation that, as soon as the first break in continuity due to beginning breakdown of tuberculous tissue occurs at these sites of high tension, the tissue will be torn apart and a minimal defect made into a cavity. The phenomenon has been compared with a run in a stretched stocking. The size of the cavity produced will depend on the extent of the tension, as well as the amount of reserve lung tissue

available in the surrounding of the lesion. In the tapering upper half of the lungs reserve tissue becomes less and less, hence cavities are most frequent and largest here, as compared with their incidence and size in the lower half of the lungs.

Air-pocket (bleb) formation due to overstretching by excess intrapulmonary tension undoubtedly plays an important rôle in pathological processes of the lung, of which tuberculosis is the most prominent and frequent one. There exists now an abundance of literature with reports on observations of rapid appearance and disappearance of such intrapulmonary and subpleural air accumulations. In subacute pulmonary conditions of childhood the picture is more striking. The pediatrics literature was recently reviewed by Zarfl (7), who applied the name of "pneumatocele" to this formation. The air is supposedly drawn in through a tear in the finer tissues of the lung. Histological evidence of such a tear could not, however, be found, perhaps because it is so minimal that it eludes histological search, but chiefly because the air-pockets themselves usually escape postmortem demonstration. The cases usually do not come to autopsy unless the condition progresses to a fatal end, in which case actual destruction and excavation has long obliterated the part of the lung in which the air-pocket existed at an earlier phase of the process. However, besides those cases of Huebschmann observed in acute tuberculous conditions, postmortem evidence of the same process can be quoted from the recent report of a series of cases studied by Orsos (8). This worker demonstrates the acute development of huge interstitial and subpleural blebs in patients with extensive pulmonary processes as produced by dyspnoeic overstretching of the lungs due to different complications which embarrassed the breathing rather suddenly. This excellent study indicates the force of thoracic traction and the damage wrought by it in the overstretched diseased lung.

Overstretching of the lung units surrounding affected areas has long been recognized in pathology. The term "emphysema tuberculosis" has been applied by pathologists to describe that picture in which disseminated lesions are being spread apart in the lung by distention of intervening pulmonary tissue. Also, emphysematous bullae and subpleural blebs in pulmonary tissue adjacent to lesions or their scars are a much-mentioned finding.

The effect of this is, however, not always a source of trouble; the same mechanism which plays such a paramount rôle in the making may become effective in the unmaking of cavities. The over-expansion of

lung units surrounding the lesions will counteract the effect of the pulmonary tension upon these lesions. Acute infiltrations surrounding fresh lung lesions are usually nonspecific in nature and tend to become absorbed quite rapidly. As soon as these lung units become again available for expansion, the tension upon the focus is relieved, the excess pull upon the tissue defect ceases, the overdistended cavity diminishes in size. The emphysematous hyperdistention of surrounding lung units may act now as a barrier against the focus within, and the result frequently is that healing gets under way, and eventually the tissue defect becomes obliterated altogether. In cases of scattered lesions, hyperdistention of intervening lung tissue counteracts intrapulmonary tension and lessens danger of extension. Besides, by keeping the foci apart, it prevents their coalescence and their breaking down into larger tissue defects. Where a basal cavity already exists, bullous overdistention of surrounding lung units aids the natural process of cirrhotic shrinkage, and thereby favors closure of the cavity, which could not be accomplished unless pulmonary tension keeps the cavity patent.

SUMMARY

The interaction between the two factors, the pathological and the mechanical processes, in the production and healing of cavities may from the above be summarized as follows:

1. The mechanical is an important responsible factor for the predilection of the upper-lung areas to cavity-formation, but in the actual production of the cavity the factor of tissue destruction plays a paramount rôle. In the subsequent turn of events, the two factors may interplay in such a manner as to both shape the course of evolution and determine the extent of the cavity to be produced, or they may come to oppose one another.

2. Thus, both tissue destruction and mechanical overstretching may tend to increase the cavitation. There may be present a reparative tissue process tending to heal the cavity, which is, however, opposed by the mechanical tension keeping the cavity patent. On the other hand, there may arise emphysema of the surrounding lung units, which relieves the overstretching and promotes the reparative tissue process.

REFERENCES

(1) HUEBSCHMANN, P.: Pathologisch Anatomie der Tuberkulose, Julius Springer, Berlin, 1928.

(2) BARAT, E.: Ein Versuch zur Erklärung der Ringschatten, Beitr. Klin. Tuberk., 1929, lxxii, 668.
(3) ORSOS, F.: Die mechanische Disposition der Lungenspitzen zur Tuberkulose, Ibid., 1928, lxx, 4.
(4) LOESCHCKE, H.: Pathologische Anatomie der Yungenspiten Tuberkulose, Ergebn. gesamt. Tuberkulose-Forschung, 1931, ii, 83.
(5) PARODI, F.: La mechanique pulmonaire, Masson & Cie, Paris, 1933.
(6) HUEBSCHMANN, P. Über Kavernen und Pseudo-Kavernen, Beitr. Klin. Tuberk., 1927, lxvii, 186.
(7) ZARFL, M.: Zur Kenntniss der gaschwulstformigen Luftsammlungen, Pneumatocelen in Brustraum, Ztschr. f. Kinderheilk., 1932, liv, 92.
(8) ORSOS, F.: Pleura-Ablation mit suppleuralen Rissen der Lungengeweber, etc., Beitr. z. path. Anat., 1933, xcii, 175.

THE PERMEABILITY OF PAPER SPUTUM NAPKINS

FRANK L. JENNINGS[1]

After the discovery that tubercle bacilli might be discharged from the mouth and nose of a tuberculous individual during coughing or sneezing, it was thought that masks for the patients would solve the problem of droplet infection. The impracticability of this method was soon evident and the more satisfactory procedure of teaching the patient to cover the mouth and nose with a handkerchief was advocated.

As gauze was cheaper than handkerchiefs and could be destroyed after use, it soon became the substance which tuberculous individuals were taught to hold before the mouth. More recently, paper napkins have largely replaced the use of gauze. That paper napkins are an improvement over the gauze from a sanitary point of view, few will deny, and, for that reason, as well as for their economy, they have largely been adopted. The manufacturer has improved these napkins, making them softer and less irritating, and has also made them more readily accessible to the patient, until now we have one soft crepe paper napkin made available to the patient in a dispenser which simulates the dispenser used for paper towels. The buyer of these sputum napkins, whether patient or business manager, is much impressed with this new method because of the readiness with which napkins may be grasped and the economy of using only one napkin each time instead of several.

The manufacturer has not considered sputum napkins from the bacteriological side, and it is from this point of view that we became interested. We wished to determine how much protection sputum napkins really offer. The interest now taken in the tuberculous infection of nurses and employees of sanatoria makes it necessary for us to test our procedures to be sure that they are as effective as possible.

In Glen Lake Sanatorium, within the last eighteen months, we have had three different changes of sputum napkins, and each change has been to a type somewhat softer than the preceding, and therefore considered

[1] Glen Lake Sanatorium, Oak Terrace, Minnesota, and the Department of Medicine University of Minnesota, Minneapolis, Minnesota.

better. It was these napkins, together with two kinds of cosmetic (removal) tissue, that we set out to examine more closely. Our approach to the problem of permeability was as follows:

1: Ascertain the number of holes in different qualities of napkins
2: Ascertain whether or not organisms could be transmitted through sputum napkins by a spray method
3: Ascertain whether organisms could be forced through by coughing.

COUNTING OF HOLES

Paper (sputum) napkins under the microscope present something of a lace-work appearance, and it was the number of these openings or holes per sq. cm. that were counted in three grades of sputum napkins and in two cosmetic (removal) tissues, the latter of which we had seen some of our patients using instead of napkins. The counts were made with a binocular, wide-range, low-power microscope, and only perforations through which light was clearly transmitted were counted. Counts were made on several napkins of the same variety and also on different areas of the same napkin. Counts were also made of two thicknesses of napkins, as many patients use one napkin folded, or sometimes two napkins. As there was practically no difference between counts of the two cosmetic (removal) tissues, they will be considered together as variety no. 1500. The varieties of sputum napkins are designated *200*, *400* and *WR*.

Their respective hole count was as follows: Napkin 200 averaged 191 per sq. cm. for one thickness, and for two thicknesses 32. Napkin W.R. averaged 265 for one thickness and 30 for two thicknesses. Napkin 400 averaged 402 holes for one thickness and 125 for two thicknesses. Napkins 1500 averaged 1,750 for one thickness and 650 holes for two thicknesses.

The size of the holes is as important as the number when considering a napkin from the standpoint of a protective agent, and therefore attention was paid to the diameter of the holes. It was found that it varied from 20 to 100 micra for the three different types of napkins, but for the cosmetic tissues (variety *1500*) the size of the holes was 25 to 800 micra. Two thicknesses reduced the size (15 to 40 micra) for the three types of napkins and for the cosmetic tissue 20 to 100 micra. Lange (1), in studying the sputum of tuberculosis patients found that "the greatest (droplets) seldom exceed 20 micra in diameter, with an occasional one

between 20 and 100 micra." He quotes Strauss who feels that droplets are seldom more than 10 micra.

SPRAYING EXPERIMENTS

We tested each type of napkin by spraying bacilli against it to ascertain the amount of reduction afforded by the napkin in relation to the size and number of holes.

The set-up was as follows: (1) a suspension of *Bacillus prodigiosus*[2] was sprayed with a DeVilbis no. 15 atomizer on to a petri dish containing nutrient agar, this serving as a control; (2) one thickness of napkin was interposed between spray and media; (3) two thicknesses of napkin interposed; and (4) three thicknesses of napkins interposed. The petri dishes were held vertically, one inch from the tip of the atomizer. The bulb of the atomizer was squeezed forcibly once before each dish, and the force exerted was found to be about the same as that exerted by a man coughing. All napkins were sterilized and kept sterile until actually used.

Following the above procedure, on January 2, 1934, a saline suspension, containing 86,000,000 bacilli per cc. (culture method), was sprayed against napkins 200, 400, WR and 1500.

With one thickness of napkin covering the media, it was found that the number of colonies on each dish was too numerous to count. When two and three thicknesses of napkin 200 covered the media, the colony count was 50 and 9 respectively. Two thicknesses of the napkin WR showed 150 colonies, while with three thicknesses there was no growth on media. Two and three thicknesses of napkin 400 showed 135 and 9 colonies, respectively, on the media. Napkin 1500 had the greatest number of holes and also the largest-size holes, and it was therefore not surprising to find the greatest number of colonies on the media when three thicknesses of napkin gave a colony-count of 350, while, with two thicknesses, the colonies were too numerous to count.

This work was repeated several times and corresponding results obtained each time. Thinking that a saline suspension might not be a fair comparison with saliva, a solution of acacia with the same specific gravity as saliva (1.004) was used, but no significant difference was noted.

Because some institutions still provide their patients with gauze to be used to cover their mouth and nose when they cough or sneeze, it seemed

[2] Culture furnished by A. T. Henricci, University of Minnesota.

advisable to compare gauze and sputum napkins. This was done by the spray method. Gauze with 12 by 20 threads per square inch was compared with napkin WR. As the accompanying photograph shows, one thickness of sputum napkin was nearly as effective in inhibiting the transmission of organisms as ten thicknesses of gauze, while two thicknesses of sputum napkins were far superior.

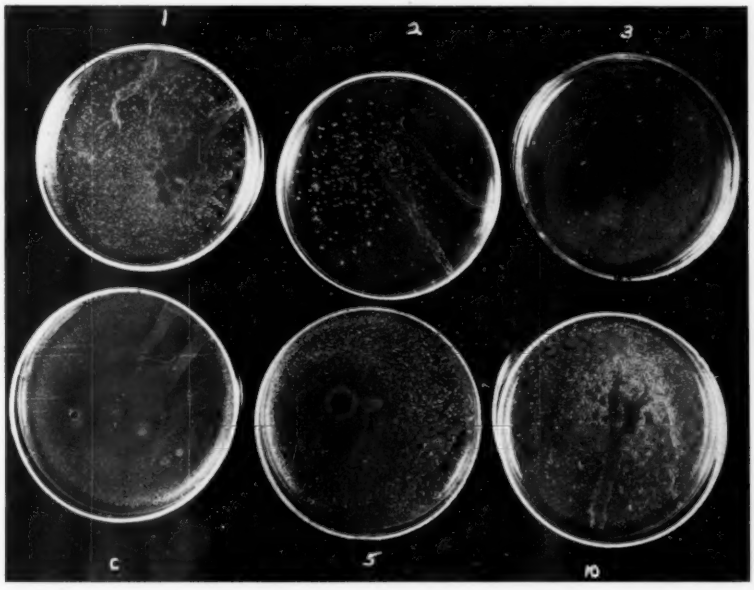


FIG. 1. Comparison of number of organisms sprayed through one, two and three thicknesses of paper napkins (upper row) and five and ten thicknesses of gauze (lower row): *C* = control

As gauze was so ineffective, no further work was done with it. The spraying procedures showed that organisms could be forced through sputum napkins. The question then arose: Are organisms forced through by the act of coughing?

COUGHING EXPERIMENTS

People who were chosen for this part of the work had bronchiectasis, acute respiratory disease, or no known respiratory disease. No patients with pulmonary tuberculosis were chosen because of the difficulty of

growing tubercle bacilli, and also because it was assumed that if other organisms could be transmitted through sputum napkins, tubercle bacilli could also be.

The set-up was as follows: Petri dishes of culture media were held perpendicularly in front of subjects' mouths, at a distance of one inch. The subjects were instructed to cough twice into each dish, whether or not napkins were interposed between media and the individuals. The dishes were held before subject's mouth in the following order: (1) with no napkin between media and subject; (2) with one thickness of napkin interposed; (3) with two thicknesses interposed; and (4) with no napkin between media and subject.

Care was taken to avoid air contamination and all napkins were sterilized prior to use, the same as in the spraying experiments. Only two varieties of napkins were used in the coughing experiments, the 400 and the WR. One reason for this was that the spraying had shown that organisms could be transmitted through all varieties, the 1500 variety allowing the greatest number, and the 200 variety the smallest number. Another reason was that the 200 variety could no longer be obtained at the sanatorium or the mill.

The following three tables are illustrative of the results obtained in many trials. Blood-agar media did not prove to be any better suited to this work than nutrient, or dextrose agar, and subjects with acute colds showed no higher percentage colony growth than is shown in the included tables:

Data of October 14, 1933

Media, one set nutrient agar; another set, dextrose-agar. Napkins, 400 variety; readings, 24, 48 and 96 hours. Numerals denote number of colonies. Subjects, normal men

SUBJECT	NO NAPKIN	1 THICKNESS	2 THICKNESSES	NO NAPKIN
		Nutrient agar		
J.	0	0	1	2
F.	1	1	0	3
L. S.	0	1	0	9
		Dextrose-agar		
J.	0	0	0	1
F.	0			1
L. S.	0	0	0	2

Data of October 19, 1933

Media, nutrient agar, dextrose-agar. Napkins, 400; readings, 24, 48 and 96 hours. Subjects W., M. and N. S. have bronchiectasis; J. is normal. Numerals denote number of colonies

SUBJECT	NO NAPKIN	1 THICKNESS	2 THICKNESSES	NO NAPKINS
		Nutrient-agar		
W.	42	1	5	2
M.	0	1	1	3
N. S.	1	2	0	0
J.	3	0	0	1
		Dextrose-agar		
W.	41	3	0	Too numerous to count
M.	1	0	0	0
N. S.	0	0	0	0
J.	3	1	2	1

Data of October 25, 1933

Media, nutrient agar and dextrose-agar. Subjects W. and N. S. have bronchiectasis; J. and R. normal. Napkins, 400 variety; readings, 24, 48 and 96 hours. Numerals denote numbers of colonies

SUBJECT	NO NAPKIN	1 THICKNESS	2 THICKNESSES	NO NAPKIN
		Nutrient-agar		
R.	12	0	2	1
J.	0	2	0	1
N. S.	2	1	0	0
W.	1	1	0	1
		Dextrose-agar		
R.	0	1	0	0
J.	0	0	0	0
N. S.	0	0	0	0
W.	0	0	0	0

The spraying experiments showed that with an increasing number of thicknesses of sputum napkins between the atomizer containing a known organism and a suitable media, there was a progressive decrease in the number of organisms which passed through the napkin. This progressive diminution is not brought out in the coughing experiments because not all coughs eject organisms. There is not only a variation in the number of

organisms given off at different times, but there is a variation in the number given off by different individuals. This variation was also observed by Ziesche (4), while attempting to count tubercle bacilli. Another factor which undoubtedly accounted for the variable number of organisms given off has been brought to light by Weaver (2), who found that a patient who coughed with his mouth wide open did not throw out as many organisms as one who coughed with his lips closed, allowing only the expulsive force of the cough to force the lips apart.

The coughing experiments showed that organisms may be forced through one and two thicknesses of paper napkins.

DISCUSSION

Because of the difficulty of growing tubercle bacilli, we made no effort to recover them. It is our opinion that tubercle bacilli can be forced through sputum napkins the same as other organisms.

Flügge, Heyman and Chausse (3) have shown that tubercle bacilli could be found not only in the mucopurulent material in mouths, but in the saliva as well of patients with pulmonary tuberculosis. Ziesche (4) counted the number of tubercle bacilli in mouth and bronchial droplets thrown out by 22 patients. In the 13 patients who showed positive results, the number of organisms varied from 3 to over 20,000 in an area of 324 sq. cm.

It has been shown that even one thickness of paper napkin decreases materially the transmission of *Bacillus prodigiosus* and that three thicknesses almost completely prevent this transmission. Two thicknesses (the manner in which it is marketed) of cosmetic (removal) tissue allow a considerable number of organisms to be forced through and for that reason should not be used by people with pulmonary tuberculosis.

One thickness of sputum napkins has been shown to be nearly as effective in filtering out organisms as ten thicknesses of gauze (20 x 12). When one considers the fact that gauze is used for a whole or part of a day and that napkins are discarded immediately after being held over the mouth, paper sputum napkins appear to be much more sanitary, in fact, the most satisfactory article we have for use in preventing organisms from being disseminated by cough or sneeze. It is hoped that the makers of sputum napkins will be able to make a napkin which will be entirely impervious to bacteria and still be so soft that it will not irritate. Until such time, it is recommended that at least two thicknesses of sputum napkins be used by tuberculous patients.

The writer is indebted to Dr. C. C. Van Winkle for many helpful suggestions and to L. Smith for technical assistance.

REFERENCES

(1) LANGE, B.: Ztschr. f. Hyg., 1926, cvi, 1.
(2) WEAVER, G.: Jour. Infect. Disease, 1919, xxiv, 218.
(3) FLÜGGE, HEYMAN, B., AND CHAUSSE, P.: Quoted by Calmette: Tubercle bacillus infection and tuberculosis in man and animals, p. 153.
(4) ZIESCHE, H.: Ztschr. f. Hyg., 1907, lvii, 50.

RAW SPLEEN EXTRACT IN TUBERCULOSIS

G. F. WATSON[1]

The rôle of the spleen in chronic infection of various kinds engaged my attention some years ago, and the enlargement which occurs in certain of these conditions suggested the possibility that this enlargement was part of a natural reaction in an attempt to combat the infection. This suggested that the spleen contains some active principle necessary to successful resistance, and, with this in mind, I proceeded to work out a method, using this property of splenic tissue in the treatment of tuberculosis.

Search of the literature revealed the fact that the use of splenic tissue had been tried at various times as an addition to the diet of tuberculosis patients. Alcoholic and other extracts had also been attempted. None of these procedures had proved successful. No one, however, had attempted the injection of raw-spleen extract. A preliminary report was made in the *Canadian Medical Association Journal*, 1930 (1).

The purpose of this article is to report the results obtained in a series of experiments carried out during the last four years on guinea pigs. The general procedure has been to inoculate the animals with an emulsion of tubercle bacilli subcutaneously in the right groin and to treat them with subcutaneous injections of spleen extract in the left groin.

In February, 1931, forty-eight guinea pigs, averaging in weight about 225 gm., were divided into two groups of equal weight. One group was given two preliminary doses of spleen extract and nine days later all were inoculated with tubercle bacilli. The treated series were given $\frac{3}{8}$ cc. of spleen extract every second day. By May 9, or 65 days after inoculation, 4 treated and 21 untreated animals were dead, or 83.3 per cent of those treated were living as compared with 12.5 per cent of the untreated.

Each guinea pig in both series was autopsied and showed generalized tuberculosis (2).

In another experiment of October, 1931, ten guinea pigs, averaging 300 gm. in weight, were placed in one large pen. Five of these were given three doses of 0.5 cc. of spleen extract previous to inoculation with tubercle bacilli and three doses of 0.5 cc. after inoculation. The amount

[1] Kitchener, Ontario.

of tubercle-bacillus emulsion used was 0.25 cc. Nine weeks after inoculation all the untreated guinea pigs were dead and all the treated ones were living. Each guinea pig when autopsied showed generalized tuberculosis.

This work was discussed with Dr. I. H. Erb, Pathologist of the Hospital for Sick Children, Toronto; and he kindly offered laboratory accommodation and coöperation in carrying out subsequent experiments. Four experiments were performed in this laboratory, all showing the treated guinea pigs living longer than the controls. On May 2, 1932, twenty-six guinea pigs were selected, 13 whose weight totalled 3,526 gm. and 13 whose weight totalled 3,488 gm. The first group were given 2 cc. of spleen

TABLE 1

NUMBER OF GUINEA PIGS	AVERAGE WEIGHT ON MAY 2, 1932	AVERAGE WEIGHT ON MAY 11, 1932 WHEN INOCULATED WITH TUBERCLE BACILLI	NUMBER OF SURVIVALS 76 DAYS AFTER INOCULATION	AVERAGE WEIGHT 76 DAYS AFTER INOCULATION	TOTAL DAYS OF SURVIVAL	AVERAGE DAYS OF SURVIVAL	POSTMORTEM FINDINGS
	gm.	gm.		gm.			
Controls, 13	268	315	2	290	765	58	Generalized tuberculosis
Spleen-treated, 13	271	329	9	375	1,165	89	Generalized tuberculosis

extract three times a week. All were inoculated on May 11th. On July 26, nine treated animals were living. Their average weight was 375 gm. or an average gain of 104 gm. Only two control animals survived the 76 days. Their average weight was 360 gm. or a gain of 102 gm. The treated guinea pigs lived 1,165 days and the controls 765 days (table 1).

On October 2, 1932, twenty guinea pigs were used, 10 whose total weight was 3,434 gm., and 10 whose total weight was 3,421 gm. The first group were given 5 cc. of spleen extract three times a week. On November 25 all were inoculated by Dr. Erb, using 0.25 cc. of emulsion of tubercle bacilli prepared as before. All were weighed at frequent intervals and their weight recorded. On March 2 the treated guinea pigs weighed 7,468 gm. and the controls weighed 5,252 gm. The latter were

shaggy in appearance and less active than the treated guinea pigs. They also felt soft, while the treated animals were firm and appeared healthy. Spleen injections were discontinued on March 15. On May 17, nine treated animals were alive and their weight was 6,884 gm.; 3 controls were alive and their total weight was 1,362 grams. The guinea pig lost from the treated group became infected at the site of the spleen injections during the first week after inoculation with some organism other than the tubercle bacillus. It never weighed more than 544 gm. This group of treated guinea pigs lived 2,502 days after inoculation, and the control guinea pigs 1,609 days after inoculation. The treated animals lived an average of three months longer than the controls (table 2).

TABLE 2

NUMBER OF GUINEA PIGS	AVERAGE WEIGHT OCTOBER 2, 1932	AVERAGE WEIGHT NOVEMBER 25, 1932 WHEN INOCULATED WITH TUBERCLE BACILLI	NUMBER OF SURVIVALS 173 DAYS AFTER INOCULATION	AVERAGE WEIGHT 173 DAYS AFTER INOCULATION	AVERAGE DAYS OF SURVIVAL AFTER INOCULATION	POSTMORTEM FINDINGS
	gm.	*gm.*		*gm.*		
Controls, 10.....	342	426	3	454	160	Generalized tuberculosis
Spleen-treated, 10.....	343	456	9	764	250	Generalized tuberculosis

The results were better in this than in the previous experiment, evidently because the inoculating dose of tubercle bacilli was smaller than in the earlier experiments. The dose of spleen was larger and the guinea pigs were more mature. Nine guinea pigs of each group in this experiment were about 350 gm. at the beginning and 425 to 450 gm. at the time of inoculation with tubercle bacilli. The other guinea pig in each group weighed about 700 gm. Another of the same weight and from the same litter was not treated with spleen or inoculated with tubercle bacilli. Weight changes in these animals are shown in chart 1.

A, B, and C are guinea pigs of 700, 720 and 720 gm. A and C were inoculated November 25, 1932, as mentioned above. A was treated with spleen extract, gained 308 gm., and lived 297 days. B was from the same litter as A and C, but was not inoculated with tubercle bacilli or treated with spleen extract and shows a gain of 257 gm. C was inocu-

lated on November 25, but was not treated with the extract. This guinea pig did not gain, became soft and shaggy in appearance and died

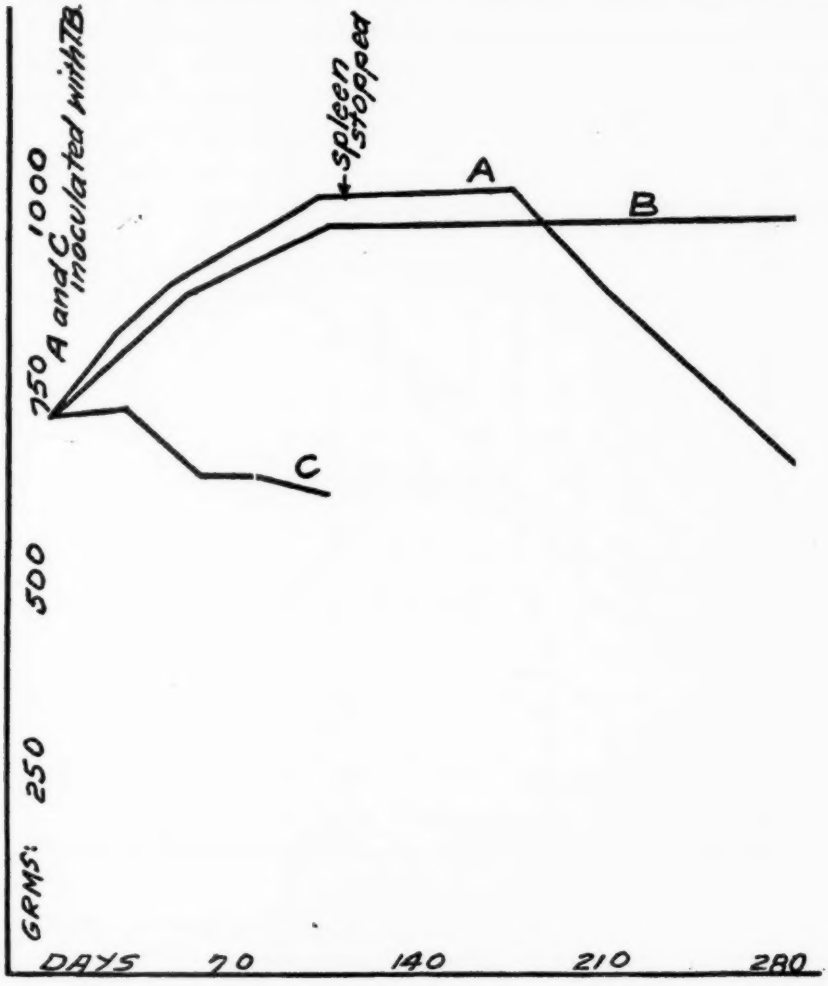


CHART 1

A. Inoculated with tubercle bacilli and treated with spleen extract
B. Growth-curve of normal guinea pig
C. Inoculated with tubercle bacilli, but not treated with spleen extract

on April 6, living 133 days after inoculation. A and C at autopsy showed generalized tuberculosis.

Chart 2: D, no. 497, is an average control and E, no. 445, is an average

treated guinea pig of the experiment described above, beginning October 2, 1932. D gained 294 gm. and survived 162 days after inoculation. E gained 614 gm. and survived 256 days after inoculation. At autopsy both animals showed generalized tuberculosis.

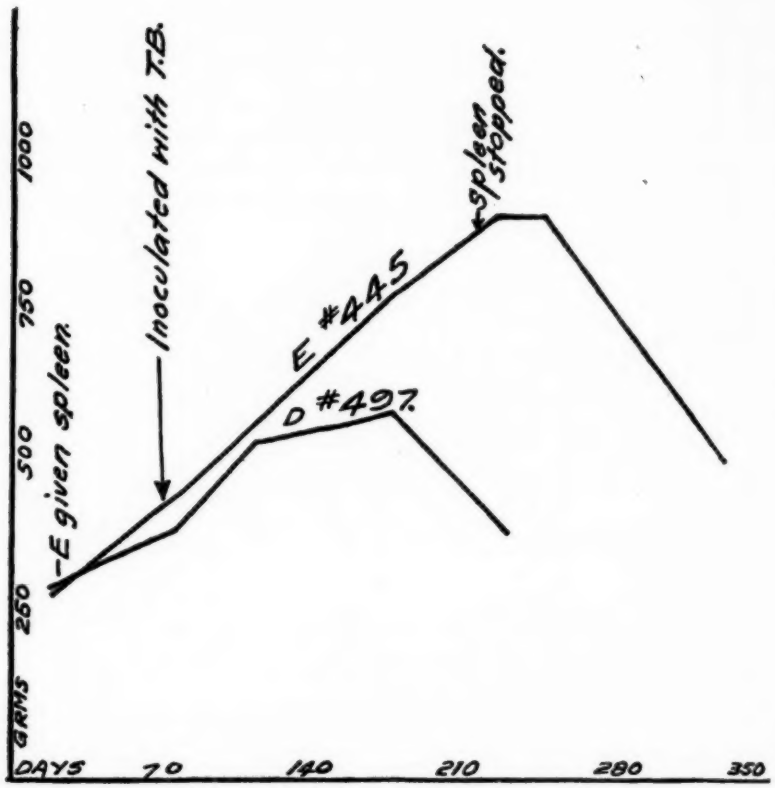


CHART 2

D. No. 497: not treated with spleen extract
E. No. 445: treated with spleen extract

A similar experiment was done at the Western Ontario Medical School in London, using fully grown guinea pigs and a larger dose of spleen extract. On August 25, 1933, eight guinea pigs, whose average weight was 806 gm., and 14 others, whose average weight was 811 gm., were selected by the laboratory attendant and placed in separate pens. Those to be treated with spleen extract were given 6 cc. of the extract twice a week, and on September 13 all were inoculated, as in the previous experi-

ments by Dr. J. H. Fisher, Professor of Bacteriology. Three weeks later all guinea pigs had palpable lymph nodes, about the size of a small bean, at the site of inoculation. Apparently the inoculating dose was larger or the organisms more active than in the preceding experiment. On November 11 there was a tremendous difference between the treated animals and the controls. The former were firm, had a healthy appearance and were maintaining their weight. The latter were soft, had a shaggy appearance and were losing weight rapidly. Spleen treatment was stopped on November 20. On December 18, all the treated guinea

TABLE 3

NUMBER OF GUINEA PIGS	AVERAGE WEIGHT SEPTEMBER 13, 1933 WHEN INOCULATED WITH TUBERCLE BACILLI	NUMBER OF SURVIVALS 96 DAYS AFTER INOCULATION	AVERAGE WEIGHT 96 DAYS AFTER INOCULATION	NUMBER OF SURVIVALS 120 DAYS AFTER INOCULATION	AVERAGE WEIGHT 120 DAYS AFTER INOCULATION	NUMBER OF SURVIVALS 200 DAYS AFTER INOCULATION	AVERAGE WEIGHT 200 DAYS AFTER INOCULATION	TOTAL DAYS OF SURVIVAL	AVERAGE DAYS OF SURVIVAL	POSTMORTEM FINDINGS
	gm.		gm.		gm.		gm.			
Controls, 8.....	811	3	552	0	—	—	—	750	93	Generalized tuberculosis
Spleen-treated, 8.....	806	8	855	7	765	4	881	1,514	189	Generalized tuberculosis (2 still living)

pigs were alive and their average weight was 855 gm. Three controls were alive and their average weight was 552 gm. On January 10 all the controls were dead. Seven of the eight treated ones were alive and their average weight was 765 gm. (table 3).

In these experiments the spleen treatment was carried on until the controls began to fail rapidly. In the last experiment, however, the treatment was continued with two guinea pigs. The weight changes of these and their controls from the same litter, are shown in chart 3. A and B are controls, showing a gradual loss in weight.

A lived until January 10, and was the last guinea pig of 14 controls.

C and D were treated at intervals. On December 12, C was treated, but not D. The former gained and the latter lost in weight. On January 10 and 19, each was given 5 cc. of a modified extract. On January 25, C had gained 100 gm. and D had gained 74 gm., and at 170 days after the last control guinea pig died, they are maintaining their weight and appear to be healthy.

The lymph nodes at the site of inoculation, which were about the size of a small marble in November and December, 1932, are now in July, 1934,

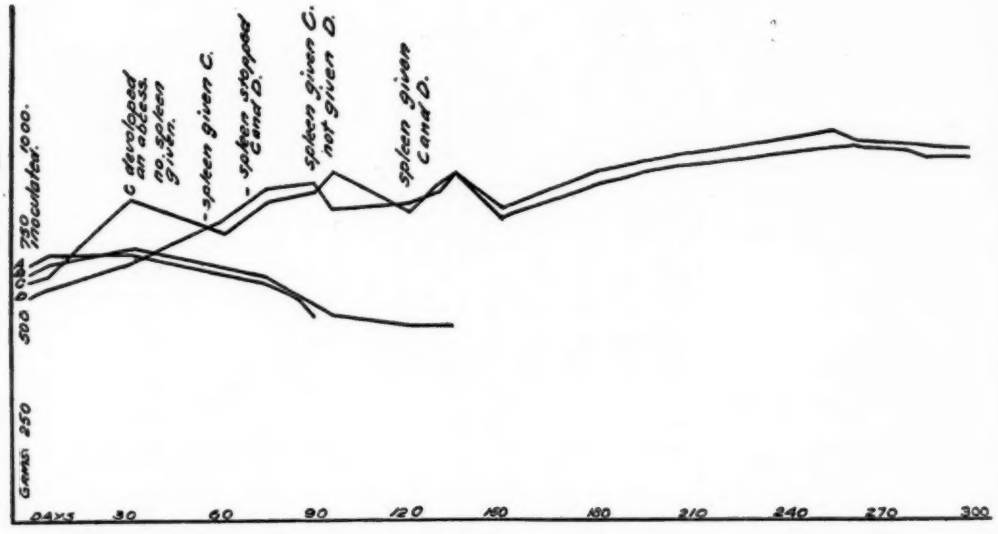


CHART 3

A & *B*. Not treated with spleen extract
C & *D*. Treated with spleen extract

like those of normal guinea pigs. Spleen treatment will be continued with these animals.

The strain of tuberculosis used in the 1932 and 1933 experiments was the Davis strain, obtained from Dr. A. L. McNabb of the Ontario Department of Health Laboratories.

On March 13, 1934, eight guinea pigs, each weighing about 450 gm. were selected at Kitchener, Ontario. Each was inoculated as before with 2 cc. of urine from a patient known to have renal tuberculosis and to have had 2 positive guinea-pig tests. On April 7, all showed large lymph nodes at the site of inoculation. Spleen treatment was begun at this

time with 4 guinea pigs, giving 5 cc. once a week. All were killed and autopsied on June 26. The controls showed extensive tuberculosis of the spleen, liver and lungs. The treated guinea pigs did not show tuberculosis of the liver or lungs.

In two of the treated animals, a few small areas of tuberculosis were present in the spleen.

The clinical cases, blood findings and histology will be reported at a later date.

The thanks of the author are due Dr. I. H. Erb, Pathologist of the Hospital for Sick Children, Toronto, for laboratory accommodation and coöperation in this work. The author is also deeply indebted to the staff of the University of Western Ontario Medical School, particularly Dr. J. H. Fisher, for their assistance.

REFERENCES

(1) WATSON: Spleen therapy in tuberculosis, Canadian Med. Assoc. Jour., 1930, xxii, 31.
(2) WATSON: Fresh raw aqueous spleen extract in tuberculosis, Proc. Soc. Exper. Biol. & Med., 1931, xxix, 13.

A NEW TECHNIQUE FOR OLEOTHORAX

T. C. LIU[1]

The problems of introducing large quantities of an oil of high viscosity into the pleural cavity are the following: (1) The cannula or trocar through which the oil has to pass must be neither so narrow as to offer high resistance against the oil current, nor so wide as to cause a wound big enough to allow the oil to regurgitate into the subcutaneous tissue after the instrument is removed and, especially in empyemata, possibly help to establish a pleural fistula. (2) The trocar should at any moment allow exact measurements of the air-pressure in the pleural cavity and the removal of the surplus air; otherwise a second needle must be introduced for this purpose (this procedure is still used by Bernou and other French authors). (3) The instrument by which the oil is pumped in should be constructed so that the injection can be made with the least possible effort.

Various instruments have been used to pump oil into the pleural cavity. Kuess[2] uses a pump with two cocks, through one of which the oil is aspirated into the syringe, and through the other it is injected into the pleural cavity. Waltuch uses a simple Record syringe of 20-cc. capacity which, each time, has to be dismounted from the cannula for refilling. Another objection to using this syringe is that so much physical exertion is required to press the oil forward, even when warmed, that it is difficult to hold the cannula steady. The disadvantages of Waltuch's cannula have been pointed out by Bume. Thomsen has constructed a syringe with a three-way cock through which he can fill the syringe, inject the oil into the chest and, by connecting it to a water manometer, measure the intrathoracic air-pressure. The disadvantages of using a syringe to pump oil through a needle of 1.5-mm. diameter (as Thomsen does) are that much force is required and it is difficult and often impossible to measure the air-pressure through a cannula constantly filled with oil. Another disadvantage of this apparatus is that there is no way to measure the oil-pressure, if or when the pleural cavity has been

[1] Division of Tuberculosis, The National College of Medicine of Shanghai, China.

[2] Quoted from Dumarest and Brette.

evacuated of all or nearly all of the pneumothorax-air. Bume's double cylinder, when used in combination with his trocar, offers an improvement in driving the oil forward: the oil is poured into the inner container and its temperature kept constant by filling the external vessel with water at 37°C. The oil is pushed forward by means of an ordinary rubber bulb. The apparatus has the disadvantage of every glass instrument, that is, easy breakage; besides, it requires an extra clamp to close the connecting rubber tube until it can be mounted on the trocar.

The purpose of this article is to describe a new method which the author has used for some time for the purpose of replacing air in the pleural cavity with oil, and found to present marked advantages over those other methods.

The instruments required are a trocar, a pump, an oil manometer, a water manometer, and a graduated vessel. The first three articles require brief description.

The trocar is one previously described by Bume and is pictured in figure 1. Its shaft is oval in cross-section (4.8 mm.: 1.6 mm.), instead of round, and contains two lumina, a wider one for the passage of oil (figure 1a) and a narrow one for air (figure 1b). Both are provided with cocks. The wider lumen has a three-way cock (figure 1, H), while the narrower lumen has a one-way cock. A stilet (figure 1S) with a removable sheath (figure 1St) is fitted into the wider lumen. At the place where the two lumina diverge from each other the shaft of the trocar is provided with a fixation plate (figure 1P).

The pump is one described by VanAllen and Wang for pneumothorax-therapy (see figure 2), and it functions on the "milking" principle.

The pump consists of a wheel 14 cm in diameter mounted vertically with shaft and bearings upon a base. A driving handle is attached to the shaft. A number of rollers are mounted at regular intervals along the periphery of the wheel, and they meet and press against a rubber tube which lies in a semicircular track below the wheel and is fastened to short metal tubes at both ends of the track. Each metal tube has two arms for outside connection, one of which extends to the back and is guarded by a stop-cock. An automatic counter records the number of revolutions of the wheel. Pumping is accomplished by turning the handle, when the rollers drive the air [or, in our case the oil] in the tube ahead continuously and the elastic recoil of the tube draws more air in behind. The direction of pumping can be reversed merely by turning the handle backwards. (VanAllen.)

The oil manometer consists of a glass tube of 25-cm. length and approximately 7 mm. width (figure 2) mounted vertically on a simple stand. It bears a mark in the middle.

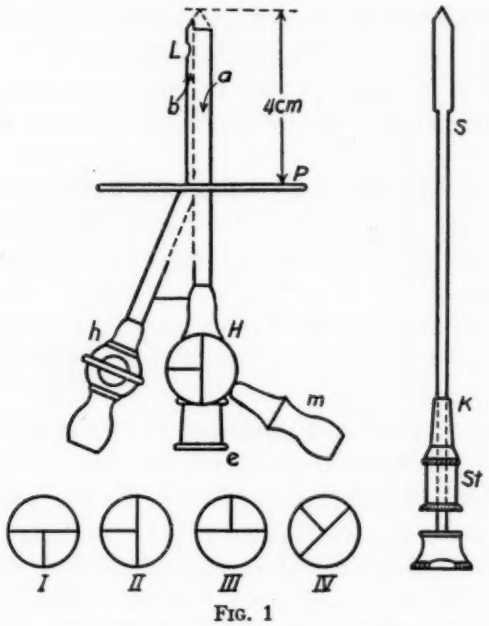


FIG. 1

Bume's trocar, reproduced from Beitr. Klin. Tuberk., 1932, vol. lxxix

a—wide lumen of the trocar
b—narrow lumen of the trocar
L—opening of the narrow lumen
h—stop-cock of the narrow lumen
H—three-way-cock
e—opening to be connected with pump
m—opening to be connected with oil manometer
S—stilet
St—sheath of stilet
K—mounting conus of stilet
I, II, III, IV—positions of the three-way cock.

The water manometer (for measuring the air-pressure) has also been described by VanAllen. It is mounted on the pump (see figure 2).

The apparatus is prepared for use as follows: (see figure 2). A rubber tube is attached to one end of the pump and an adapter to the other end of this tube. The free end of the pump is connected to the oil container by another rubber tube and a two-way cock (figure 2). The lateral

opening of the wide lumen of the trocar (figure 1m) is joined with the oil manometer by a third rubber tube. The narrow lumen of the trocar is connected to the water manometer by a fourth piece of rubber tubing.

Manner of Use: The patient should lie on his back or on the side opposite to that to be treated, so as comfortably to expose the site selected for the insertion of the trocar. Local anaesthesia is then applied and

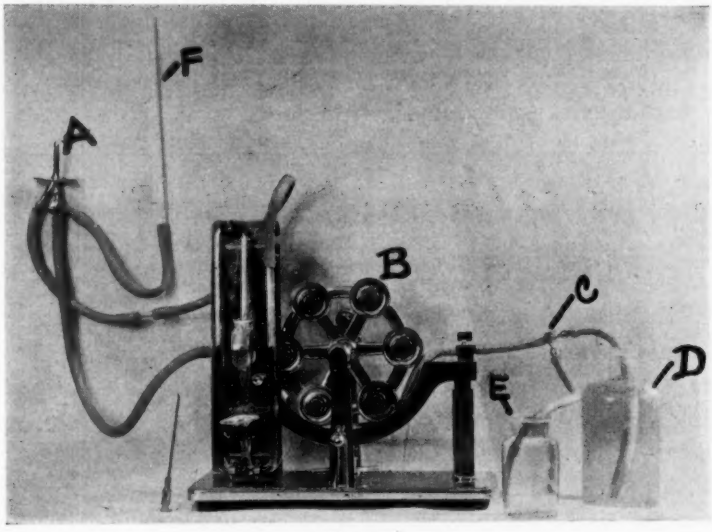


FIG. 2

Complete Outfit for Oleothorax

A—trocar
B—pump with water-manometer
C—two-way cock
D—graduated oil vessel
E—discard vessel
F—oil-manometer

the operating field prepared in the usual way. The trocar is introduced into the chest so that the long diameter of its shaft is at right angles to the ribs. The stilet is withdrawn into its sheath until the automatic arrest and the three-way cock is closed (figure 1, position IV). The trocar is now fixed in its position by means of strips of adhesive tape across the fixation plate. The one-way cock is then opened, and fluctuations of the water manometer looked for as an indication that the trocar has entered the pleural cavity. If the fluctuations are present, the stilet

and its sheath are dismounted and replaced by the above mentioned adapter connecting the trocar with the pump (figure 2). The three-way cock is then turned into the position connecting the pump with the oil manometer (figure 1, position I). The latter is filled with oil to the mark by a few turns of the pump-handle. Then, by turning the three-way cock, connection is established between the pump and the wide lumen of the trocar (figure 1, position II). The oil is introduced into the pleural cavity by slowly turning the pump-handle, under constant observation of the fluctuations of the water-manometer, which will soon register an increase of pressure. When the air-pressure has thus reached a slightly positive value, some air must be removed. This is done by simply turning the pump-handle backwards, after having turned the two-way cock on the tube between the pump and the oil container (figure 2D) so as to close the way to the latter and to open the tube to the outside. It is, however, of advantage to connect this end of the cock to a discard vessel (figure 2E), which will collect the small amount of oil which is still in the pump and precedes the air in coming out.

When the evacuation of air decreases the air-pressure in the pleural cavity slightly below atmospheric pressure, as indicated on the water manometer, the two-way cock is again turned toward the oil container and the direction of pumping is once more reversed. These steps are repeated until the desired amount of oil has been injected; or until the oil level in the pleural cavity has risen so high as to obstruct the opening of the narrow lumen of the trocar when further measurements of air-pressure are impossible and measurements of the oil-pressure must take their place. The oil-pressure is measured by turning the three-way cock so as to connect the oil in the pleural cavity with the oil manometer (figure 1, position III). As the oil from the chest rises in the manometer, the latter is adjusted in height so as to bring the mark on the tube opposite the meniscus of the oil. When the meniscus comes to rest, its vertical distance from the level of the trocar is measured and recorded in centimetres as the oil-pressure, using the plus sign if the meniscus is above the trocar and the negative sign if the meniscus is below. It is desirable to take such measurements after the injection of each 50 cc. of oil.

When the desired quantity of oil has been injected, the trocar is withdrawn. It is advisable to cover the wound by a compressive bandage which may be removed after 12 to 24 hours.

The small air-bubble which remains above the oil level in the pleural

cavity always absorbs rather quickly and is, by some, considered an advantage because the greater compressibility of air acts as a buffer in case of ensuing effusions.

We use gomenolized paraffine oil, and, before introducing larger quantities, we test the sensitiveness of the pleura by first injecting 10 cc. and a few days later 50 cc. of the oil. Only if no considerable reactions have been noticed, do we proceed to fill the pleural cavity, usually in two or three sittings. For the test-injections we use an ordinary tapping cannula.

In a fairly big number of oil-fillings this technique has rendered satisfactory results and has not led to any complications attributable to the method.

BIBLIOGRAPHY

(1) Bernou, A.: Contribution a l'etude des injections huileuses massives dans la plèvre, Rev. Tuberc., 1926, 3S. (7), 345.

(2) Bernou, A.: Des décompressions anomales du poumon au cours du pneumothorax artificiel, Ibid., 1928, ix, 75.

(3) Bernou, A.: Quelques remarques sur la technique des blocages huileux de la plèvre, Ibid., 1928, ix, 742.

(4) Bernou, A.: Quelques remarques concernant les oléothorax, Gaz. Méd. France, 1929, iii, 52; 1929, iii, 95.

(5) Bume, G. F.: Einige technische Neuerungen bei Anlegung des Oleothorax und bei der Pleuraspülung, Beitr. Klin. Tuberk., 1932, lxxix, 782.

(6) Diehl, K.: Doppelseitiger Pneumothorax und Oleothorax und ihre Technik, Ibid., 1928, lxviii, 173.

(7) Diehl, K.: Die physikalischen und physiologischen Grundlagen des Oleothorax und ihre Folgerungen für die Klinik, Ztschr. Tuberk., 1929, liii, 514.

(8) Dumarest, F., and Brette, P.: La pratique du Pneumothorax et de la Collapsothérapie chirurgicale, Paris, 1929.

(9) Thomsen: Ein neuer Apparat für die Oleothoraxtherapie als Ergänzung zur Pneumothoraxapparatur, Beitr. Klin. Tuberk., 1930, lxxv, 491.

(10) VanAllen, C. M.: A pump for clinical and laboratory purposes which employs the milking principle, Jour. Am. Med. Assn., 1932, xcviii, 1805.

(11) Waltuch, E.: Zur Indication und Technik des Oleothorax, Ztschr. Tuberk., 1931 lx, 144.

(12) Wang, T. T., and van Allen, C. M.: Pump and manometer for administering artificial pneumothorax, Jour. Am. Med. Assn., 1932, xcix, 561.

ALLERGY AS A GUIDE IN TERMINATING ARTIFICIAL PNEUMOTHORAX

JOHN R. NEAL[1]

For many years, in fact since the discovery of the benefits of the use of artificial pneumothorax in treating pulmonary tuberculosis, it has been a puzzling question among phthisiologists just how long to continue the treatments. Each worker has used his judgment, depending more or less upon his own experience. This course usually produces good and lasting results, but there are times when cessation of the compression therapy and allowing the lung to reëxpand has been disastrous to the patient. A search of the literature shows voluminous material regarding the type and stage of case in which to start the treatment, but the writer has been unable to find a great deal regarding the perplexing subject of when to stop it. The material found shows somewhat conflicting opinions among the writers, and I have found no one who has devoted an entire paper to the subject. So it is with some hesitancy that I have undertaken to review some of the literature and advance what we believe to be an entirely new method of procedure in determining when artificial pneumothorax should be stopped in some cases.

Fishberg (1) states,

> After a pneumothorax has been maintained for several months and the patient has been symptom free, the problem of allowing the lung to re-expand should be given serious consideration. The interval between refills should be extended and the quantity of air insufflated at each filling reduced and if constitutional symptoms do not increase, the temperature and pulse remain normal and graded exercises are not effective in producing symptoms of toxemia, the intervals between refills are further extended and the quantity of air insufflated at each filling reduced. Treated in this manner quite a number of cases can be terminated in one year.

He further stated he has "not allowed a pneumothorax to remain for more than three years."

Ruben (2) concludes,

> Pneumothorax improves the condition of many patients with pulmonary tuberculosis who otherwise would very likely not have done so well. Quite frequently

[1] Los Angeles, California.

collapse of the lung even partly successful helps the individual to lead a normal, although somewhat sheltered life, the individual is still tuberculous and subject to all the vicissitudes of disease. At the present time in comparatively few does it result in full clinical recovery in the sense that the tuberculous process undergoes complete absorption and calcification. It is hazardous to speak of cure under any condition when reactivation is liable to occur at any time during the life of the patient.

We cannot agree with the last statement for we have all seen many patients who have had collapse therapy living normal lives, carrying on with their work and having no recurrence of tuberculous disease.

Myers (3) states,

The question which artificial pneumothorax patients most frequently ask the clinician is "When may I discontinue the treatment?" Unfortunately, symptoms, physical signs and x-ray films are not safe criteria in answering this question. No one can determine with certainty when the tuberculous lesion is so well under control that it will not reactivate if allowed to re-expand. In the earlier days of this work, the lung was usually allowed to re-expand too soon. The disappearance of symptoms and the marked improvement in the patient's general condition led to a false sense of security on the part of the patient as well as the physician. Experience soon taught us, however, that if permanent results were to be obtained, the lung should be collapsed over a long period. No one can lay down a rule as to just how long the treatment should be continued. This is a problem that must be solved for each individual patient. It must depend on several factors, such as the extent of disease when the treatment is instituted, size of cavities, presence of tubercle bacilli in the sputum, tuberculous and non-tuberculous complications and the patient's general condition. In minimal lesions one hesitates to allow the lung to re-expand in less than two years. In moderately advanced or far advanced cases the lung should be kept collapsed for a period of at least three to five years, and in many much longer. In fact, when large cavities are present and the involvement is extensive on the institution of treatment, it is doubtful whether the lung should ever be allowed to re-expand. The red cell sedimentation rate, as recommended by Cutter, may prove a valuable index on this subject. He is of the opinion that by observing this rate carefully and periodically throughout the course of treatment, one can determine with a reasonable degree of accuracy when the lesion is well under control.

Dumarest (4) is of the opinion that successful pneumothorax should be continued indefinitely while Rist (5) believes that the minimum duration of treatment should be five years.

Packard (6) concludes that an effective pneumothorax of two years' duration and negative sputum for at least one year give reasonable assurance that the lung may be reëxpanded with safety.

Amberson (7) concludes, "Cessation of pneumothorax depends on original state of lesion, size of excavation, and that, if the lung was satisfactorily collapsed and cavities kept closed for from eighteen months to two years, it is safe to allow the lung to re-expand."

Mills (8), reviewing a work by Bocquet on this subject says,

> The author in deciding whether to terminate a successful pneumothorax states the following points are of importance: first, the character of the initial lesion; second, the efficiency of the collapse; third, the rapidity of the effects, quick disappearance of symptoms means rapid and solid healing; fourth, incidents occurring in the course of healing. Pleural effusions may hasten healing. New lesions appearing should cause postponement of termination. Fifth, the general condition of the patient, absence of malaise and ability to work are of great importance. He further states that as to a time limit the point of departure is the permanent disappearance of tubercle bacilli from the sputum, and that generally at least four years should elapse from the time tubercle bacilli disappear before discontinuing treatment.

These opinions agree in most factors and have been the practice of the writer for many years. However, since I had seen apparently excellent results from only a few months' treatment by this method, I began to wonder whether or not there might be a method of procedure whereby we could be fairly sure which of these cases came under this type, and thus be able to discontinue the collapse therapy much sooner than had heretofore been done: also, whether or not other patients who had had pneumothorax over a long period of time could safely discontinue the treatments.

We were doing a great many tuberculin tests in contact and noncontact children in the clinics of the Los Angeles County Health Department under the direction of Dr. John L. Pomeroy, County Health Officer, and Dr. P. K. Telford, chief of the tuberculosis division, and since it became my duty to carry on the continued collapse therapy of the discharged patients from Olive View Sanatorium and the Los Angeles County General Hospital, also patients of private physicians (who were financially unable to continue under private care), I became more interested in getting these patients back to a status of an economic asset rather than a liability, and decided that, if we considered patients who had a negative

reaction to the intracutaneous tuberculin test as nontuberculous, why not test those getting artificial-pneumothorax treatments. Some say, "But you are dealing with adults and a large majority of them will give positive results." We have not found this to be true; for we are using the test on all cases presenting pulmonary disease difficult to differentiate from pulmonary tuberculosis, as well as on all adult contacts presenting no physical evidence of disease, and slightly more than 50 per cent show positive skin tests. Of course, those who present physical signs not characteristic of tuberculous disease and a positive skin reaction to tuberculin are still a problem for diagnosis. But as to those who show a negative tuberculin reaction to the higher dosages of the test, we feel we are safe in saying that we are not dealing with tuberculosis.

In making this study a group of 30 cases was selected. These patients had been having treatments over a period of from eight months to eight years. All were above 17 years of age, ranging from 17 to 45 years, and 50 per cent were in the third decade of life. There were 11 males and 19 females. All were proved cases of pulmonary tuberculosis, having sputum positive for acid-fast bacilli and X-ray evidences characteristic and interpreted as tuberculosis with cavity. Twenty-one of these cases were former patients of Olive View Sanatorium, the other nine being from other institutions and from private physicians. Cutter's series of dilutions of tuberculin were used and the potency of each solution was tested on known positive reactors before being used. Each patient was given 0.1 cc. or 0.001 mgm. tuberculin intracutaneously on the flexor surface of the forearm and was inspected at 48-hour, 72-hour and one week intervals before proceeding with the higher dosage. If negative, the patients were given the next higher dosage, or 0.01 mgm., and inspected in the same manner. This procedure was followed until a maximum of 10 mgm. of tuberculin was used. Of course, those showing positive reactions were eliminated from the higher dosages. The results of these tests were as follows: 6 showed positive reactions to the first test, 3 to the second, 10 to the third, 1 to the fourth, and 2 to 10 mgm. tuberculin, leaving a group of 8 showing negative reactions to the highest dosage used.

Studying this group of negative reactors as to the time collapse therapy had been employed, we find one patient each for 11 months, 14 months, 17 months, 2 years, 3 years, 3½ years, 3 years 9 months, and 4 years, respectively.

Pneumothorax treatments were discontinued and the patients watched

closely by fluoroscopic examinations and when the lung had almost expanded they were tested a second time, using only the 1-mgm. and 10-mgm. dosages. Only one of these 8 patients showed a positive reaction to 10 mgm. tuberculin, and refills were immediately started before the lung had fully expanded and become adherent to the chest-wall. This case was one that had had treatments for only 11 months, and whose cavity had been collapsed only 6 months. An interesting feature regarding this case is the fact that she is a contact to a sister who has active pulmonary tuberculosis with positive sputum and was undiagnosed until after the second testing. The other seven are still negative to 10 mgm. tuberculin after six months' time and after complete reëxpansion of the lung, none of the X-rays being interpreted as showing "pathological activity."

Further analysis of these cases as to type and extent of disease or size of cavities will not be made, for we believe that a patient under collapse therapy, who loses his allergy to tuberculin and whose lung is allowed to reëxpand, is safe regardless of the extent of the original lesion. However, the writer realizes that six months is a rather short period of observation, since cessation of treatment and the series of cases is small, but we believe it is worthy of further study and opens up a new field for further investigation. We believe also that by using the tuberculin test we may be able to discontinue collapse therapy much sooner in from 25 to 30 per cent of cases now under treatment. We also realize that those cases showing a positive reaction still present the same problem and need the careful consideration we have always used in determining the time pneumothorax can be safely discontinued.

BIBLIOGRAPHY

(1) Fishberg: Pulmonary tuberculosis, 1932, ii, pp. 549–550.
(2) Ruben: Am. J. M. Sc., January, 1933, p. 737.
(3) Myers: Artificial pneumothorax, Jour. Am. Med. Ass., October 27, 1934, p. 1299.
(4) Dumarest and Brette: La pratique du pneumothorax, Masson & Cie, 1929.
(5) Rist: Quand faut el interrompre le pneumothorax, Therapeut. Rev. Tuberc., 1930, ix, 915.
(6) Packard: Journal Thorac. Surg., 1932, i, 581.
(7) Amberson: Artificial pneumothorax treatments, Annals Int. Med., 1930, iv, 343.
(8) Mills: Review of Book by Bocquet: La cessation et les resultats eloignes du pneumothorax artificiel, Amer. Rev. Tuberc., 1933, xxviii, 153.

THE INTRACUTANEOUS TUBERCULIN TEST AND USE OF THE FLUOROSCOPE IN A COUNTY SURVEY[1]

G. W. WEBER, K. M. MURPHY AND F. W. HOLCOMB

The literature which has been published in the last few years on tuberculin-testing, substantiated by numerous statistics, would seem to render superfluous yet another publication corroborating its usefulness. But lately two papers, appearing in the May and June issues of the *American Journal of Public Health*, the first by Dr. Robert E. Plunkett, Director of Tuberculosis, New York State Department of Health, and the second by Dr. H. E. Kleinschmidt, Director of Health Education of the National Tuberculosis Association, suggest how the test may be given with added value and efficiency. Since our work has some points of contact with their suggestions, we submit the report of sixteen months of tuberculin tests in this County.

Dr. Plunkett, while not belittling the importance of the test among school-children, raises his authoritative voice to warn against the indiscriminate way in which the test may be used, especially when public funds are involved. He says:

> Too many workers in tuberculosis have been diverted from case-finding work in the fertile field of cases, contacts and doubtful cases, to the less productive and the more expensive method of case-finding among school-children. Unless the home and contacts of every reactor are studied epidemiologically, little, if anything, is really achieved.

Let us analyze the work of these investigators and follow the procedure usually adopted by them in their survey. First, these surveys are most often begun as a result of some special endowment which may last one or two years, and therefore they never have the character of permanence. Second, they are usually carried on only in some particular section of a town or among a selected group of children, and therefore they are seldom general. Third, they do not emphasize the importance of personal contact with the parents, who are left, as Dr. Plunkett puts it, in a state of "apprehension and confusion which tends to lead them to become

[1] From the Ulster County Tuberculosis Hospital, Kingston, New York.

pathological minded." Fourth, and most important, being limited to the children only, these surveys do not take into account the source of contact, which is so essential in the control of tuberculosis.

All the positive reactors are X-rayed. Sometimes it is only one X-ray, sometimes two; and in some surveys a total of three X-rays per positive reactor has been used. The ones who show hilar involvement and calcifications are classified with the different names of juvenile, childhood, hilar tuberculosis, etc.

Probably a very small percentage of the subjects is sent to preventoria, but the great majority is kept in school. Nobody seems to pay much attention to the positive reactors who show neither hilar nor pulmonary lesions. However, the sole fact that they are allergic proves that they have been or are being infected, and are as much in need of care as the others.

Dr. Kleinschmidt says:

> For the majority of children with childhood type lesions the serious danger confronting them is not the lesion *per se*, but continuous exposure if such exists. Until that question has been cleared up and until the contact, if it is established, is broken, the child is to be regarded as being in danger of developing serious tuberculous disease.

If it is true that childhood tuberculosis is the forerunner of adult tuberculosis, it is also true that the adult case, in order to develop, needs not only favorable conditions of the soil, but also the presence of the bacillus. Although some authors, especially in France, believe that in most of the cases this reinfection is autogenous, and therefore only a reactivation of the apparently healed childhood lesion, there is no doubt in our mind that the continuous contact plays the greatest rôle in the development of the adult tuberculosis.

Therefore, it is, in our opinion, a mistake to concentrate all the effort in the discovery of childhood tuberculosis alone. While so much is done for this kind of lesion, which is the result of an infection, why is nothing being done in order to trace the adult open case, which is, after all, the cause of the infection in the child? It is as a result of continuous contact that later the child, when in his teens, will change the picture and show an adult lesion. In other words, why give so much importance to the effect and neglect the cause? When we discover an adult active case we go after the contacts and keep them under our supervision. Why not reverse the procedure and supervise all the adult contacts of a child positive reactor?

Now to present our procedure and its results in this territory. Ulster County is on the shore of the Hudson, midway between New York and Albany. It is almost quadrangular in shape with an area of 1,173 square miles, and its population of about 80,000 inhabitants is partly industrial and partly rural. The county seat, Kingston, has a population of 30,000; in addition there are four townships ranging from 2,000 to 6,000 inhabitants. The rest of the population is sparsely settled in rural communities. Therefore we have a mixed population to work with. The mortality for tuberculosis in 1932 was 80.7 per 100,000, and this county was among six with the highest mortality in New York State.

Our survey can be divided into two periods. In the first one, from February to May 1933, we tested 742 children with a resulting figure of 238 positive reactors. This high percentage was largely due to the fact that 137 were known contacts. Most of them were X-rayed either by us or by the State Clinic, and the plates showed a few with childhood lesions, a few with suspicious shadows, but only one with a definite adult minimal lesion. This X-raying of all positive reactors was too expensive to fit into our budget, and further consideration of this procedure was out of the question, more especially since we planned to examine the parents of the grade-school positive reactors as well as the children themselves.

During the summer we tried paper films, and, although the results were very satisfactory, we still could not effect enough economy. The use of the paper films may be practical in schools with a large registration, where in one day 500 or 600 pupils can be X-rayed, but for our schools, in some of which we had only a few reactors, this method is unsuitable. The only way left to us was *via* the fluoroscope. Widely used in Europe as a means of detection, the fluoroscope is seldom employed in that capacity in this country, although we believe that it fulfills this purpose admirably, provided one has had some experience with it. We always leaned on the doubtful side in the sense that we X-rayed anyone who showed the least suspicious shadow under fluoroscopic examination, and thus we probably took more plates than were necessary. Then again, no doubt a few cases with lesions may have escaped our detection, but we do not believe that they were many or very important, because as a rule we were able to discover very small subapical lesions.

Meanwhile, we continued with the work of propaganda. Since our people knew nothing about the test, except for the State tuberculin survey of the dairy herds, we gave numerous lectures to the Parent-Teachers' Associations, the Kiwanis, Rotary and Grange Clubs, and to

any other civic organization which cared to listen to us. Most of the time we supplemented the lectures with X-ray pictures. Further, the local press coöperated by publishing periodically small items of propaganda furnished by us.

Thus, in October, 1933, feeling that enough propaganda had been done to ensure us a measure of success, we started the second period of our survey, which lasted until May, 1934. We went back to the same schools and as a preliminary step each child was given a consent-blank by the school nurse, with a letter to the parent in which was explained the purpose of the test, its harmlessness, and the fact that it had been endorsed by the Medical, State and Federal authorities. The parents then had to fill out the consent-blank indicating the name, age of the child, and the name of the family physician, and return it to the school-nurse through the child. When all the blanks had been collected we went to the school to give the test. We always preferred the Mantoux (intracutaneous) as being in our opinion speedier and more accurate. The reaction was read after 48 hours, and this was done most rapidly by going into the class-rooms and checking on our lists the names of the positive reactors. We did not pay much attention to the degree of the reaction, and it is possible that we may have considered as positive some cases showing only a slight redness without oedema. To each positive reactor of the grade-schools we gave another letter for his parents, in which we said that a positive reaction did not necessarily mean that the child had active tuberculosis, but it only proved that he had been or was at the time in contact with some adult who had the disease, and therefore it was especially advisable for the parents themselves to be examined at our clinic. For the high-school students we made arrangements with the school principals for their transportation to the clinic. All students able and willing to pay for their fare were grouped together, twenty-five at a time, for the bus chartered to convey them to and from the Hospital, and in this way they lost relatively little time from their classes. It must be said that most of them paid their own fare, which for the furthest school was only thirty cents apiece.

Our clinics were held three times a week, on Mondays and Wednesdays, from 9 to 12 A.M. and on Saturday from 9 A.M. to 5 P.M. Occasionally they were overcrowded, but we were able to take care of the number each time. The only complicated part was the keeping of the various records.

The results of the tuberculin test for both groups are given in table 1.

TABLE 1

Children tested in period from October, 1933, to May, 1934

	REGISTRATION	CONSENTS	PER CENT	POSITIVE REACTORS	PER CENT
High-schools	3,070	1,362	44	446	32.7
Grade-schools	6,254	3,596	56.5	533	14.5

The percentage in the grade-schools is not high, but by adding the consents obtained the previous year when we tested the known contacts, the figure is brought up to 60 per cent. We feel that this is a fairly good showing, since we used no pressure other than the first letter to obtain that number, and without doubt a large majority of those parents who hesitated this year will be willing to coöperate next year.

We found when working on the statistics that the number of consents was in direct proportion to the interest taken by the school authorities, and we know now that, if they are convinced as to the value of the test, the way is open. This was especially true in the rural districts where there is a closer relationship between parents and teacher, and where her opinion is considered more seriously; in fact, in two country schools where no preparatory work of propaganda had been done, we obtained practically 100 per cent of consents. Since we are convinced that in field-work the most important ally is the teacher, we have inaugurated a course of lectures to the students of the State Normal School in this county, and also to the District Teachers' meetings.

Among the high-school students, we met with the same experience which was reported by Paul Wakefield of the Chadwick Clinics, namely, a very low percentage of consents. In our largest school, having a registration of 1,800, only 743 consents were brought in, or a percentage of 41. Here the principal allowed us only 40 minutes every morning during assembly time to do the test, and although we tried, with the coöperation of the school-physician, to do as many as possible each session, it took several days to complete the list. While on the first day the consents were numerous, they gradually decreased during the following days, as the students, seeing some of the reactions, began to avoid the test for fear of having an arm temporarily sore or incapacitated. We think that, if we had been allowed to perform the test all in one day, the percentage would have been much higher, as it was in other smaller schools.

Of the 446 high-school students who were positive reactors, we examined and fluoroscoped 410, or 92 per cent. Of the 533 grade-school

pupils who were positive, 23, with their parents, were examined and X-rayed by the State Clinic as being known contacts; one died, and 5 moved from their communities soon after the test, so that altogether we have to account for 504 reactors. Of these, 393, or 78 per cent, were examined and fluoroscoped. In all, 803 pupils of both groups were fluoroscoped, and of these, ninety-nine, or 12 per cent, were X-rayed. The X-ray findings are given in table 2.

TABLE 2

	ADULT-TYPE TUBERCULOSIS			CALCIFICATIONS	SUSPICIOUS	OTHER CONDITIONS
	Minimal	Moderately advanced	Advanced			
Grade-schools	1	1	1	10	4	3
High-schools	3	2		9	4	2
Totals	4	3	1	19	8	5

Under the heading "with calcifications" we have included all those who showed either hilar or parenchymal calcified lesions. Under the heading "suspicious" we have classified those children whose X-rays, although suspicious (fibrous bands, pleural effusions) did not warrant a definite diagnosis, either for childhood or for adult-type of tuberculosis. Under the heading "other conditions" we have classified two with scoliosis, one with an enlargement of the heart, one with a nontubercular basal infection, and one with numerous calcifications of the cervical lymph nodes. As far as "childhood tuberculosis" is concerned, (we have avoided using this term as a classification), we have detected fewer cases, certainly, than others who have used the X-ray system. This was due not to the fact that we failed to see calcifications, but because we decided at the beginning not to record these healed primary lesions unless they were extensive and numerous. The percentage of the adult type discovered by us is perhaps higher than that found by other investigators; for instance, Dr. Kleinschmidt reports that the Chadwick Clinics discovered 0.65 per cent cases, or an average of one case out of 154 positive reactors who were X-rayed, aged 15 to 19. Our percentage is instead nearly 1 per cent of the children examined, aged 5 to 20.

For the 393 grade-school pupils we tried, in so far as was possible, to discover the source of contact in each case, and we were successful with

about half of them. In order to make our figures clearer, we have divided the group into three categories:

1: Direct contact: One or more members of the immediate family tuberculous and in constant associations with the child: 141 cases.
2: Occasional contact: A neighbor or a boarder having the disease: 28 cases.
3: Doubtful contact: Case-history in the family, but direct contact with the child denied: 20 cases.

This leaves 204 cases, or 52 per cent, with the source of infection untraced: 89 of this number had brothers and sisters who were negative to the test, so that we may assume that some of them could have picked up the infection outside of the home. Again, as we have said before, it is possible that we have classified a few children as positive who were not. In two communities it was very difficult for us to trace the sources of contact. One is considered as a health-resort and many families take in boarders; in the other, which is in a rural district, we were surprised to have as high as 34 per cent positive reactors, and although, so far, we have had the opportunity of examining only 17 of them, for only three could we establish a direct source of contact. We have learned that the tuberculin-testing of the herds in that particular locality, completed last year, showed a higher percentage of positive cows than elsewhere in the county. Without drawing any conclusion, we think it is interesting to report the fact, also because J. A. Myers reports that Broker, in a township of Minnesota, where all the cattle had been tuberculin-negative, found only one positive reactor out of 160 girls and boys tested.

In searching for the information we were after, we were often met with great reluctance on the part of those questioned to admit ever having had a relative with tuberculosis. The idea that this disease in the family is some kind of a disgrace is held especially by the Italian element, and often it took the most persistent questioning and tact to uncover the fact. In most of the cases the contact had been broken for years by the death of the diseased person, and therefore we emphasized only the necessity for periodical check-ups. In the cases in which the contact, unrecorded, was still living, we warned the parents of the dangers to which the children were exposed, and the urgency for breaking the contact as soon as possible.

We come now to the parents, and for explanatory purposes we have divided the families into two groups:

1: "Completely examined:" In this group we have classified the children whose parents came to the Clinic, with any other adult living in the house. Here we have also included 45 children, one of whose parents was dead. Total: 271 children, or 54 per cent, of the positive reactors—comprising 217 families.

2: "Partially examined:" In this group we have classified the children who came with only one parent or other adult member of the family. We have also included here 20 children, one of whose parents was absent, either because of residence outside the County, for reasons of work, or because of divorce, so that we could not easily reach him. Total: 122 children, or 24 per cent—comprising 104 families.

Of the first group 416 adults, and of the second group 121 adults, a total of 537, were examined and fluoroscoped. Of these, 64, or 12 per cent, were X-rayed. All the X-ray findings, of both parents and children, are given in table 3.

In order to have a standard reading, all the plates have been classified by Dr. William Siegal, Associate Director, Division of Tuberculosis, Department of Health, Albany, to whom we are deeply indebted, both for this and for other helpful suggestions.

TABLE 3

	EXAMINED	ADULT-TYPE OF TUBERCULOSIS			SUSPICIOUS	OTHER CONDITIONS
		Minimal	Moderately advanced	Advanced		
Grade-schools	393	1	1	1	4	3
High-schools	410	3	2		4	2
Parents	537	11	9		7	16
Totals	1340	15	12	1	15	21

The examination and interviewing of families has proved especially interesting. In one case, for instance, a family had 4 children tested, of which the two older were positive and the two younger negative. When the parents came to the Clinic, the only clue they were able to give us was that previous to the birth of the two younger children they had had a maid in their employ, who had since married and had a child of her own. Since this child was a positive reactor also, we succeeded in persuading the mother to be examined, and, not surprisingly, she proved to be a moderately advanced case of tuberculosis. In another family in

which the mother had died of tuberculosis two years earlier, the two children naturally reacted positively, and when fluoroscoped the girl showed a pleural effusion, which was, however, symptomless. The father and uncle proved healthy enough; and the only other adult member of the family was the grandmother, aged 71, who, because she was crippled, had been left outside in the car. She gave her consent to an examination, was carried in, and found to be the offender.

As is to be expected, there still remains a large number of parents to be won over to examination, and with this purpose in mind we have sent another form-letter, and also listed them for personal calls. In an effort to draw the fathers, most of whom have been either unable or unwilling to come during the day, we have opened an evening clinic on Thursdays from 7 to 9 o'clock. Thus we hope to clear the field fairly well through the course of the summer so as to resume work in the fall with all previous records brought up to date.

The final step in the outline of the survey for this year is to send to each family physician, as soon as it is available, a list of the names of his patients who have been examined at our Clinic, giving our findings, the source of contact if traced, suggestions for further care if such be necessary, and mention of any other pathological condition which might have been discovered, at the same time notifying the parent that the results of our examination have been mailed to his physician. In this way we hope to have full coöperation on the part of the medical profession in the future, and a better understanding of the work we are trying to do, as in more than one instance the parents took the positive reactor to their physician, who, after examination, declared the child healthy and further preoccupation unnecessary, thus removing him from our survey.

Our program for next year is the completion of the test in the county. So far, we have surveyed mostly the larger townships, but we are very anxious to extend our work to all the rural districts, where, we have found by experience, the number of consents is larger, the percentage of positive reactors smaller, and the chance of tracing the source of contact better. We also hope to return to the schools already surveyed to test, if possible, those whose parents failed to consent the first time. For the third-year schedule we will start anew, testing those who were negative the first year and the newly registered children. It is our ambition to develop the system in such a way that every child would be tested upon first entering school and followed throughout his entire school-life.

We do not know if this work has been tried elsewhere in just the same

way, although we do know that several investigators have tried to study the parents of the positive reactors. William G. Ryan, for example, in his survey in Rockland County among 1,885 students of the 7th and 8th grades and of the high-schools, reports having X-rayed 108 members of 53 families of positive reactors, but we do not know if this group was purposely selected because of family histories, or if it was just the beginning of a general check-up of the families. All of them, however, have used the X-ray for examination.

Nassau County has been using the fluoroscope in the schools. Up to August, 1933, they had fluoroscoped 2,969, both pupils and teachers, and X-rayed 688, or 23.1 per cent of them, with the discovery of 5 cases of adult tuberculosis. Their percentage is lower than ours, but this is because they examine all the children, having given up the tuberculin test altogether because of the low number of consents obtained. And, again, they do not try to examine the parents, except those whose children have shown lesions.

However, we believe that we have shown so far the usefulness to which the fluoroscope can be put. The percentage of cases of adult type of tuberculosis found by us among the school children compares favorably with the percentage of other investigators, and therefore proves that we cannot have missed much, although we took altogether only 163 X-rays, or 12 per cent of all the people examined.

And, undoubtedly, the discovery of 4 per cent of tuberculosis among the parents demonstrates the value of the Mantoux test when it is combined with the search for the source of infection.

That this method of survey is within reach of any community, may be seen from the following figures. Our salaries were already included in the general budget of the hospital, so that the main expenses have been:

163 X-rays averaging 75¢ each	$122.25
Printing and other small items	60.00
Total	$182.25

So far, only 54 per cent of our families have been completely examined and studied, but, considering that our results were obtained from what one might call "virgin soil," this has seemed to us an encouraging figure. Moreover, we feel justified in hoping for an ever-increasing response from the public as the work of propaganda grows. After all the solution of the problem of tuberculosis is based on these two fundamentals: early discovery of cases and education of the public.

CONCLUSIONS

A plan is given by which:

1. The value of the tuberculin test among school-children can be greatly increased through the examination of the parents and the epidemiological study of the families in an effort to trace the source of contact.

2. The use of the fluoroscope reduces to a minimum the cost of carrying on a survey, thus providing a means of detection well within the budget limitations of any community.

We wish to express our appreciation to Dr. Thomas Crowley and Dr. Leo Rosenberg, School Physicians, and to Miss Margaret Carty, X-ray technician, whose invaluable cooperation has made our survey possible.

A COMPARISON OF THE ROENTGENOLOGICAL AND PATHOLOGICAL FINDINGS IN EXPERIMENTAL PULMONARY TUBERCULOSIS IN RABBITS[1]

Part 1. Primary Tuberculosis

HUGH E. BURKE

There are two variable factors which profoundly influence the pathogenesis of pulmonary tuberculosis in man, namely, (1) the duration of infection, and (2) the number of invading organisms. These factors are largely responsible for the present confusion in the interpretation of roentgenological and pathological findings in human tuberculosis. The time of infection and the number of invading organisms can, however, be adequately controlled in experimental animals.

A roentgenological and pathological counterpart of chronic pulmonary tuberculosis in man has been produced in rabbits by the intratracheal injection of measured quantities of tubercle bacilli.

In the present paper the findings in primary experimental pulmonary tuberculosis in rabbits will be presented and discussed. In a subsequent paper the findings in secondary or reinfection experimental pulmonary tuberculosis in rabbits will be given.

PRIMARY EXPERIMENTAL PULMONARY TUBERCULOSIS

Experimental

Rabbits: All of the rabbits used in these experiments were the offspring of one pair. The close interbreeding of the animals probably produced as uniform a soil for the growth of tubercle bacilli as it is possible to obtain in the present state of knowledge. The rabbits were injected intratracheally when they were approximately 6 months old and weighed about 1,500 gm. They were practically free from snuffles and other respiratory infections common to laboratory animals. They were kept in cages indoors and offered a constant well-balanced diet throughout the period of the experiments.

Bacillary suspensions for intratracheal injections: Cultures of virulent human tubercle bacilli,[2] grown on glycerine broth of p.H. 6^2–6^6, were used for all the

[1] From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

[2] Strain H37, Saranac Laboratory.

intratracheal injections. Only cultures that showed good growth and that were from 3 to 4 weeks old were employed. The tubercle bacilli were dried between layers of filter paper and weighed. A known weight of organisms was ground in a mortar. While the grinding was proceeding a measured quantity of isotonic salt solution was added drop by drop. The suspension was diluted so that 0.25 cc. of suspension contained 1.0 mgm. of tubercle bacilli. The suspension was shaken vigorously before each rabbit was injected.

Intratracheal injections: The rabbits were anaesthetized with ether in the early experiments and with sodium amytal, administered intraperitoneally, in the later experiments. Sodium amytal proved preferable because it is more effective in preventing the animals from coughing and expelling the suspension. The trachea was exposed. The suspension of tubercle bacilli was injected into the trachea with a tuberculin syringe and needle of fine bore. The animal was then laid on the left side, with the head and forequarters elevated, so as to direct the suspension into the left lung. A lesion limited to the left lower lobe was usually produced.

Roentgenograms: Chest roentgenograms of the rabbits were made at daily, weekly and monthly intervals over periods up to 4 years. The technique employed was that recently described by Greenberg (1933). In addition, roentgenograms of the excised and inflated lungs were made at each necropsy. Many of these were taken in the negative-pressure chamber described by Burke (in press).

Autopsies: Rabbits were sacrificed at intervals such that the lesions gave a composite picture of the pathogenesis of pulmonary tuberculosis. After the gross pathological findings had been noted, roentgenograms of the excised lungs were made. Immediately following this, the lungs were distended with Zenker's fixative. Later, with the necropsy protocols, the chest roentgenograms and the roentgenograms of the excised lungs as guides, the lungs were sectioned. The majority of the sections for microscopic examination were stained with haematoxylin and eosin. A few were stained for tubercle bacilli, elastic tissue and connective tissue. Unless otherwise noted, the word, "sections," will henceforth refer only to those stained with haematoxylin and eosin. Following the examination of the pathological material the roentgenological and pathological findings were reviewed and compared.

By the method just described it is possible to produce localized pulmonary tuberculosis, which, in spite of slight variations in the soil and in the number of invading organisms, is strikingly uniform in its progress. The method affords an excellent opportunity for comparing roentgenological and pathological findings.

Before presenting the experimental findings it may be well at this point to mention briefly some of the observations of other investigators who have studied primary experimental pulmonary tuberculosis produced in animals by the intratracheal injection of tubercle bacilli.

Prudden (1894) appears to have been the first observer in this country to inject animals intratracheally with tubercle bacilli. He injected healthy rabbits with tubercle bacilli and various pyogenic bacteria, and came to the conclusion that cavities are not formed in acute pulmonary tuberculosis unless there is a concurrent infection. In 1913 Lewis and Montgomery reported their observations on experimental pulmonary tuberculosis produced in dogs by the introduction of large amounts of bovine tubercle bacilli into the lungs through a tracheal catheter. They found that, contrary to Prudden's views, cavities were formed when tubercle bacilli alone were introduced into dogs' lungs. Their experiments were of short duration. Rogers (1920) and Mullin and Ryder (1920–1921) allowed rabbits to inhale suspensions of tubercle bacilli from their upper air-passages, and studied the resulting lesions. One of Mullin and Ryder's papers contains some observations on the effect of posture on the localization of particles of india-ink and bacteria in the lungs, which the present study has confirmed. In 1921 Baldwin and Gardner published an article on experimental pulmonary tuberculosis. They employed guinea pigs infecting them with tubercle bacilli by the spray method. They killed some animals at intervals designed to permit them to follow the pathogenesis of the pulmonary lesions, and found, among other things, that resorption of the lesions required variable lengths of time, from 3 months to over 1 year. Corper (1922–1923) used large quantities of dead bovine and human tubercle bacilli to produce pulmonary tuberculosis in dogs. He obtained widespread lesions. His experiments were not of sufficient duration to permit him to study retrogression of the lesions. Soper, Sampson and Haskins (1927) appear to be the only investigators who have made a roentgenological study of primary experimental pulmonary tuberculosis. They used rabbits, instilling heavy suspensions of tubercle bacilli into the animals' nares to produce the pulmonary lesions. Most of the lesions in their rabbits, in contrast to those to be described in this paper, were progressive.

Seventy-six healthy rabbits were employed in the present study. All of the animals were injected intratracheally with 1 mgm. of virulent human tubercle bacilli (strain H37). In fourteen of the rabbits an attempt was made to localize the bacilli in the right lung. This was not successful, for at necropsy only one-third of these animals had lesions limited to the right lung. In the remaining rabbits an attempt was made to direct the bacilli into the left lung. This was successful, as the data in table 1 indicate. It was not practical to inject all of the rabbits at one time and to follow them simultaneously. Accordingly, the rabbits were handled in groups and in some groups animals were killed early and late in order to control the experiment. The results were sufficiently uniform to warrant the construction of a composite roentgenological and pathological picture of primary experimental pulmonary tuberculosis.

There was no evidence of pulmonary disease in the posteroanterior or

lateral chest roentgenograms of any of the rabbits until the 10th day. Abnormal shadows regularly appeared in the chest roentgenograms at some time between the 10th and 17th days, as the data in table 1 show. The roentgenograms of the excised lungs, however, of some of the rabbits killed before this period, contained abnormal shadows. Occasionally, there were shadows in the films of the excised lungs as early as the 2nd day. Usually there were shadows of significance in such films from the

TABLE 1

CASE NUMBERS	NUMBER OF RABBITS	LUNG SUPPOSEDLY INOCULATED	FIRST ABNORMAL SHADOW IN CHEST ROENTGENOGRAM	FIRST ABNORMAL SHADOW IN LUNG ROENTGENOGRAM	SITE OF DISEASE
			day	*day*	
5–13	9	Right	16th	6th	Both lungs
14–20	7	Left	15th	7th	Left lung
21–28	8	Left	10th (1)	2nd	Left lung with one exception
29–36	8	Left			Left lung
A			16th		
B			12th		
116–120	5	Right	(2)		Right lung
116			14th		
117			16th		
118			16th		
119			10th		
120			14th		
130–133	4	Left	(2)		Left lung
130			17th		
131			13th		
132			17th		
133			17th		

(1) Both posteroanterior and lateral roentgenograms.
(2) Roentgenograms of each rabbit made every day.

6th or 8th days forward. The abnormal shadows in the films of the excised lungs taken on the 2nd day were cast by small areas of non-specific pneumonia and large paratracheal lymph nodes, as the following protocol exemplifies:

Rabbit No. 21: Killed on the 2nd day: The roentgenograms made during life contained no abnormal shadows. The film of the excised lungs contained two shadows of note, one near the shadow of the left main bronchus and the other

near the shadow of the bifurcation of the trachea. Grossly the lungs appeared natural. The left lung, however, did not inflate to the same extent as the right lung. The paratracheal lymph nodes were moderately enlarged. The other organs presented no gross evidence of tuberculosis. The sections showed small areas of lobular pneumonia in the left lower lobe near the hilum. In several places the septa were thick. They contained some erythrocytes and dilated capillaries filled with erythrocytes, and variable numbers of small mononuclear and polymorphonuclear leucocytes. In other places the septal markings were obliterated and the alveoli were filled with polymorphonuclear leucocytes undergoing disintegration. The pulmonary lymphoid tissue adjacent to the pneumonic foci showed slight hypertrophy and hyperplasia of the reticulum. An enlarged paratracheal lymph node presented no unusual microscopic features.

Areas of nonspecific pneumonia frequently follow the introduction of foreign material into the lungs. As a rule, only a few bronchi and alveoli are implicated. The pneumonic reaction usually recedes in a few days, as the following protocols of rabbits killed on the 4th and 6th days indicate:

Rabbits Nos. 22 & 23: Killed on the 4th & 6th days: The chest roentgenograms contained no abnormal shadows. The films of the excised lungs, however, contained elliptical shadows adjacent to the outline of the trachea. Macroscopically the lungs appeared natural, but the paratracheal lymph nodes were moderately enlarged. The other viscera presented no evidence of tuberculosis. Two sections of the lungs of the rabbit killed on the 4th day showed a small lobular pneumonic focus in the apex of the left lower lobe. In this area several bronchioli and alveoli were filled with large and small mononuclear cells. Sections of other portions of this rabbit's lungs and sections of the lungs of the rabbit killed on the 6th day showed few changes. Here and there in the left lower lobe of both animals, there were isolated and clumped mononuclear leucocytes, a few polymorphonuclear leucocytes, and a little exudate. The lymphoid tissues in these localities and in the paratracheal lymph nodes showed some hypertrophy and hyperplasia. There were tubercle bacilli in many of the intraälveolar mononuclear leucocytes. (The roentgenological and pathological findings of rabbit No. 23 are shown in plate I.)

The only abnormal shadows in the roentgenograms of the excised lungs of rabbits killed on the 4th and 6th days were cast by large paratracheal lymph nodes. Although the lungs appeared natural macroscopically, the sections showed one minute pneumonic area and many isolated and clumped mononuclear cells laden with tubercle bacilli. The

latter observation proves that the tubercle bacilli injected intratracheally reached the lungs and indicates that the lesions in rabbits killed later were tuberculous.

Abnormal shadows were usually found in the roentgenograms of the excised lungs of rabbits killed between the 6th and 8th days, as the data in table 1 indicate. The roentgenological and pathological findings of a rabbit killed on the 8th day were as follows:

Rabbit No. 24: Killed on the 8th day: Both the posteroanterior and lateral chest roentgenograms of this animal failed to yield any evidence of disease. The film of the excised lungs, however, showed some irregular shadows in the right lung field and several oval shadows at the left side of the outline of the trachea. There were no macroscopic lesions on the visceral surfaces of the lungs. The paratracheal lymph nodes were unusually large. The other organs appeared natural. The sections showed a discrete and lobular pneumonic process adjacent to a large bronchus in the right lung. The bronchus was patent and intact. In the pneumonic area there were focal nodular collections of mononuclear cells which filled many alveoli and obliterated the septal markings. The centres of some of these nodules contained only cellular debris. Multinuclear giant cells of the Langhans type were present in a few such nodules. There were a few isolated nodules of a similar nature. The alveoli adjacent to these contained variable numbers of large and small mononuclear cells. The pulmonary lymphoid tissue in this area was hypertrophic. The paratracheal lymph nodes were hypertrophic and hyperplastic. The lymph sinuses, which were immensely dilated, contained lymphocytes and large mononuclear and polymorphonuclear leucocytes.

In the foregoing instance, as in others, roentgenograms of the excised lungs taken on the 8th day contained abnormal shadows, although no evidence of disease was detected in the chest roentgenograms. The shadows in the roentgenograms of the excised lungs were cast by a pneumonic focus, a few early tubercles consisting of nodular collections of mononuclear cells, and several large paratracheal lymph nodes.

The first chest roentgenograms in which signs of disease were detected, were those taken between the 10th and 17th days. The essential roentgenological and pathological findings in two rabbits killed soon after the discovery of abnormal shadows in the chest roentgenograms, were as follows:

Rabbits Nos. 25 & 26: Killed on the 10th & 12th days: The first chest roentgenograms of these animals to reveal any evidence of disease were those taken on

the 10th and the 12th day, respectively. The abnormal shadows were homogeneous. The films of the excised lungs of both rabbits contained numerous more or less sharply delineated shadows, which proved to depict the location and the size of the lesions more accurately than the chest films. There was a pyramidal area of gray gelatinous-appearing consolidation in the upper part of the left lower lobe of each rabbit. On the dorsal surface of the left lower lobe of the animal killed on the 10th day there were several pink to gray pin-head sized lesions. The lungs of both rabbits inflated readily, although the left lung of the animal killed on the 12th day did not inflate to as great a degree as usual. The paratracheal lymph nodes were gray and very large. The other organs presented no gross evidence of tuberculosis. Sections of the lungs of each rabbit showed an extensive confluent lesion at the apex of the left lower lobe and numerous discrete and confluent nodular collections of mononuclear cells distal to this lesion. In some places the septal markings were obliterated. Many of the nodular collections of mononuclear leucocytes contained one or more giant cells. Some of the smaller collections were partially surrounded by lymphocytes. In other words, typical tubercles were present. The alveoli adjacent to some of the isolated and conglomerate tubercles were distorted. They contained variable numbers of mononuclear cells. The pulmonary lymphoid tissue was hypertrophic and hyperplastic. Most of the paratracheal lymph nodes showed similar changes. One paratracheal node of the rabbit killed on the 12th day, however, contained an area of necrosis. (The roentgenological and pathological findings of rabbit 26 are illustrated in plate II.)

In the one case abnormal shadows were first detected in chest roentgenograms taken on the 10th day; in the other case, in those taken on the 12th day. In both instances the shadows were of uniform density and irregular outline. The roentgenograms of the excised lungs permitted better visualization of the location and size of the lesions than the chest films. The lungs contained isolated and conglomerate tubercles. Some of the small, isolated tubercles were surrounded by lymphocytes. There was a macroscopic area of necrosis in one of the paratracheal lymph nodes of the rabbit killed on the 12th day.

The abnormal shadows in chest roentgenograms taken between the 10th and 17th days were usually similar in size and character. However, the pulmonary lesions of rabbits killed about the 17th day occasionally contained necrotic foci. The following is the protocol of a rabbit killed on the 16th day:

Rabbit No. 28: Killed on the 16th day: The chest films contained abnormal homogeneous shadows which were similar in size and character to those of the

chest films of the rabbit killed on the 12th day. The shadows in the films of the excised lungs were large. They had both definite and indefinite margins. There was a pyramidal, gray, gelatinous-appearing area of consolidation in the upper pole of the left lower lobe. Distal to this area there were a few isolated irregularly-shaped gray foci. The lungs inflated readily, but the left lower lobe did not enlarge to the same degree as the other lobes. The paratracheal lymph nodes were soft, brown and very large. The other organs presented no gross evidence of tuberculosis. Sections showed a pneumonic area in the upper part of the left lower lobe. This area consisted of vast collections of mononuclear cells and traces of exudate. The centres of most of the larger aggregations contained nuclear material and amorphous debris. Some of the small bronchi contained polymorphonuclear leucocytes and debris. Adjacent to the large consolidated areas there were isolated tubercles. Some of these had necrotic cores; all of them were well surrounded with lymphocytes. The septa in the vicinity of these tubercles were very thick, and the intervening alveoli contained variable numbers of mononuclear and polymorphonuclear leucocytes. The pulmonary lymphoid tissue and the paratracheal lymph nodes showed changes comparable to those described in the preceding protocols.

Although the abnormal shadows in the chest roentgenograms of the rabbit killed on the 12th day were comparable to those in the chest roentgenograms of the rabbit described above, the lesions which cast the shadows were different. In the former, the shadows were cast by clusters of recent tubercles; in the latter, by clusters of well-formed tubercles some of which contained necrotic foci.

The shadows in the chest roentgenograms gradually became larger, usually attaining the greatest size at the end of the 1st month as indicated by the data in table 2. The lesions in the lungs of the rabbits underwent further changes. The following protocol describes the roentgenological and pathological findings of an animal killed in the latter part of the 1st month:

Rabbit No. 331: Killed at 3¼ weeks: Abnormal homogeneous shadows with indefinite margins were present in the left lung field of the chest roentgenograms from the 10th day forward. The film of the excised lungs contained a large homogeneous shadow, the margins of which were in part indefinite and in part definite. There were many small and several large areas of gray consolidation in the left lung. The largest of these were in a ventral lappet of the upper lobe and in the apical and diaphragmatic portions of the lower lobe. Some areas contained yellow foci suggestive of caseation. The left lung did not inflate as well as the right lung. At the height of inflation the small areas

TABLE 2

CASE NUMBERS	NUMBER OF RABBITS	APPROXIMATE DATE OF LARGEST ABNORMAL SHADOWS	APPROXIMATE DATE OF BEGINNING CLEARING OF SHADOWS	APPROXIMATE DATE OF DISAPPEARANCE OF SHADOWS	DURATION OF EXPERIMENT
328–331	4				
331		3 weeks	—	—	3 weeks
328		1 month	—	—	1 month
329		0*	0	0	1 month
330		1 month	—	—	1 month
322–327	6				
324		1 month	—	—	1 month
322†		1½ months	—	—	1½ months
327		1 month	1½ months	—	1½ months
323		3 weeks	1½ months	—	2 months
325		3 weeks	1½ months	—	2 months
326		3 weeks	1½ months	—	5 months
313–321	9				
318†		1 month	—	—	1 month
320		0	0	0	3 months
321		1 month	1½ months	3 months	3 months
313		1 month	3 months	4 months?	4 months
317		1 month	2 months	4 months	4 months
315		1 month	2 months	4 months	5 months
316		1 month	2 months	3 months	5 months
314		1 month	2 months	5 months	6 months
319		2 weeks	1 month	1½ months	6 months
298–303	6				
298		1 month	2 months	3 months	3 months
300		0	0	0	3 months
299		1 month	2 months	4 months	8 months
303		2 weeks	1 month	3 months	8 months
301		2 weeks	1 month	2 months	10 months
302		1 month	2 months	3 months	10 months
199–204	6				
199		3 weeks	1 month	1½ months	6 months
204		1 month	1½ months	4 months	1 year
202		1 month	1½ months	3 months	1 yr., 6 months
203		1 month	1½ months	3 months	1 yr., 6 months
200		1 month	1½ months	4½ months	1 yr., 9 months
201		3 weeks	1 month	2½ months	1 yr., 9 months
1–4	4				
1		2½ months	—	—	2½ months
3		9 months	—	—	9 months
2		1 month	3 months	—	3 years
4		1½ months	3 months	—	4 years

* "0" means no clearly defined evidence of disease.

† Rabbits #318 and 322 had an ulcerative bronchitis as well as pulmonary tuberculosis.

of disease were not visible and the large areas of consolidation appeared recessed in pink slightly puckered lung. There were two large soft lymph nodes on the left side of the trachea. The rest of the viscera presented no gross evidence of tuberculosis. The sections showed extensive areas of consolidation in the left lung. The consolidated areas consisted of isolated and conglomerate tubercles, the centres of many of which where necrotic and caseous. The septal markings were obliterated. Only a few blood-vessels were identified. Some appeared occluded with thrombi. A few of the bronchi contained cellular debris. The bronchial walls, however, were intact. Many of the intervening alveoli were compressed and distorted. They contained variable numbers of large mononuclear cells. The pleura overlying an area of consolidation in the left lower lobe was infiltrated with leucocytes. (The roentgenological and pathological findings of this rabbit are illustrated in plate III.)

The final chest roentgenogram of the rabbit described above contained a large uniform shadow with indefinite margins. The roentgenogram of the excised lungs also contained a large uniform shadow. The margins of the latter, however, were in part definite and in part indefinite. The shadows in both the chest films and the films of the excised lungs were cast by areas of recent tuberculous pneumonia containing many caseous foci.

There were mottled shadows rather than large homogeneous shadows in the chest roentgenograms of other rabbits. The lesions in all the rabbits killed between the 3rd and 7th weeks were similar, however, in that they contained caseous foci. The following is the protocol of an animal killed during the 7th week:

Rabbit No. 327: Killed at 6¾ weeks: The shadows in the chest roentgenograms varied from large homogeneous to mottled. The film of the excised lungs contained chiefly mottled shadows. There was an area of gray consolidation, with several minute yellow foci, in the upper pole of the left lower lobe. When the lungs were inflated in the negative-pressure chamber this portion of the left lung responded sluggishly and appeared wrinkled even at the height of inflation. Although the left lung alone contained lesions, the paratracheal lymph nodes on both sides of the trachea were large, soft and gray. The other organs appeared natural. The sections showed clusters of tubercles adjacent to the large bronchi in the upper pole of the left lower lobe and several isolated tubercles in the distal parts of the same lobe. The lesions were sharply circumscribed. Many had necrotic or caseous cores. There were polymorphonuclear leucocytes adjacent to some of the caseous foci. The alveoli adjoining the tubercles appeared unusually large. They contained, as a rule, only a few mononuclear cells. The pulmonary lymphoid tissue in the left lower lobe

was hypertrophic and hyperplastic. A paratracheal lymph node showed marked hypertrophy and hyperplasia of the reticular elements.

The foregoing protocol shows that both the chest roentgenograms and the roentgenograms of the excised lungs of one rabbit contained mottled shadows and that these shadows were cast by isolated and conglomerate tubercles undergoing caseation. The lesions in the lungs of the 9 animals killed in the latter part of the 1st month or the early part of the 2nd month, contained caseous foci. It is reasonable, therefore, to assume that all of the rabbits had, in the early stages of the disease, tuberculous lesions containing caseous foci.

Usually the shadows in the chest roentgenograms began to recede sometime between the latter part of the 1st month and the early part of the 3rd month, as the data in table 2 indicate. The lesions of rabbits killed during this period showed varied retrogressive changes. The following protocol is that of a rabbit killed at the end of the 2nd month:

Rabbit No. 323: Killed at $7\frac{6}{7}$ weeks: The abnormal shadows in the chest roentgenograms attained the greatest size at $2\frac{6}{7}$ weeks, remained the same until $4\frac{6}{7}$ weeks, and were somewhat smaller at $6\frac{3}{7}$ weeks. They were homogeneous and had indefinite margins. In the final chest film the shadows were mottled. The film of the excised lungs disclosed mottled shadows throughout most of the left lung field. At necropsy there were many gray lesions of varied size in the left lung. The largest of these lesions, situated in the apical and diaphragmatic portions of the left lower lobe, contained yellow foci. At the height of inflation these areas presented the appearance of recessed scars. The paratracheal lymph nodes were large, soft and gray. There were no macroscopic tuberculous lesions in the abdominal viscera. All of the sections taken from the left lower lobe showed tuberculous lesions. In the apical and basal portions of the lobe there were lobular pneumonic areas containing caseous foci partially surrounded by lymphocytes and fibroblasts. The interalveolar septa adjacent to these areas were thick, due to invasion with lymphocytes, mononuclear cells and fibroblasts. The intervening alveoli contained variable numbers of mononuclear leucocytes. Some of the alveoli adjacent to the visceral pleura in the vicinity of the apex of the lobe, were emphysematous. Scattered throughout the lobe there were isolated tubercles containing partially or completely walled-off caseous foci. The septa and alveoli adjacent to most of these isolated tubercles appeared natural. In one place, however, the pleura overlying a small tubercle was thick and contained many leucocytes and some fibroblasts. A pulmonary lymph node lying between the branches of a stem bronchus was large and partly caseous. The wall of one of the bronchi ad-

jacent to this node, contained many leucocytes. The paratracheal lymph nodes presented evidence of hypertrophy and hyperplasia. (The essential roentgenological and pathological findings of rabbit 323 have been reproduced in plate IV.)

According to the foregoing protocol the roentgenological evidence of pulmonary disease consisted of homogeneous shadows of varied size during most of the experiment and of mottled shadows at the end of the experiment. The increasing size of the shadows in the early serial roentgenograms indicated that the rabbit's lesions were progressing. The decreasing size of the shadows in the later roentgenograms suggested that the lesions were retrogressing. The character of the shadows, however, failed to yield satisfactory information concerning the nature of the lesions. For example, the mottled shadows in the film of the excised lungs of this rabbit were similar to the small shadows with indefinite margins in the film of the excised lungs of the rabbit killed on the 12th day, as a comparison of plates IV and II shows. Macroscopically, the lesions were comparable, as shown by the photographs of the sections in plates IV and II. Microscopically, however, the lesions were strikingly different. Those of the rabbit killed at the end of the 2nd month consisted of fibrous or fibrocaseous tubercles; those of the animal killed on the 12th day, of primitive poorly-defined tubercles.

Frequently, chest roentgenograms taken during the 3rd month presented no evidence of disease, as the data in table 2 indicate. As a rule, however, the roentgenograms of the excised lungs of rabbits killed during the 3rd month disclosed evidence of disease and the lungs contained macroscopic lesions. The following is the protocol of a rabbit killed at the end of the 3rd month:

Rabbit No. 321: Killed at 13$\frac{1}{7}$ weeks: In this instance the shadows attained greatest size at 4$\frac{5}{7}$ weeks. They had practically disappeared by 7$\frac{1}{7}$ weeks. Both posteroanterior and lateral chest roentgenograms, taken immediately before the rabbit was killed, failed to show any evidence of disease. Roentgenograms of the excised lungs, however, disclosed many finely mottled shadows in the left midlung field. A lipiodol study failed to reveal any abnormalities of the bronchi. At necropsy the right lung appeared natural. The left lung contained the following lesions: (1) a small area of red to gray consolidation in the ventral lappet of the upper lobe, and (2) many pin-point to pin-head-sized gray tubercles in the lower lobe. The paratracheal lymph nodes were very large and soft. They varied in color from gray to brown. There were no gross tuberculous lesions in the other viscera. Sections through the left

lower lobe showed many small tubercles. These were composed of lymphocytes and mononuclear leucocytes, the former predominating. Signs of necrosis and caseation were lacking. The septa near the tubercles were thick and a few of the adjoining alveoli contained large mononuclear cells. All of the lymphoid tissue in the vicinity of the tubercles was hypertrophic and hyperplastic. Sections through the left upper lobe presented a similar picture. A large bronchus in this area, however, contained cellular debris. At one place, adjacent to a tubercle, the wall of the bronchus was undergoing necrosis and ulceration. A large paratracheal lymph node presented the following features: The blood vessels were unusually prominent. The lymph sinuses were greatly dilated. The lymphoid tissue was separated into islands by vast sheets of reticulum. The interstices contained large numbers of mononuclear leucocytes and erythrocytes.

In the foregoing instance chest roentgenograms taken at the end of the 3rd month failed to reveal any evidence of disease. The roentgenograms of the excised lungs, however, contained some small shadows. These were cast by minute partially healed tubercles. It was plain from a comparison of the lesions of this rabbit with those of rabbits killed early in the course of the disease that healing by resolution and organization was taking place.

The chest roentgenograms of many of the rabbits, taken after the 3rd month, contained no abnormal shadows. The roentgenograms of the excised lungs of such rabbits sometimes gave inferential evidence of residual lesions. At other times they gave no evidence of disease although there were demonstrable lesions in the lungs. The following protocols contain the findings of two rabbits sacrificed in the 4th and 6th months respectively:

Rabbit No. 317: Killed at 17$\frac{5}{7}$ weeks: There were no abnormal shadows in any of the chest roentgenograms taken after 12$\frac{4}{7}$ weeks. The outline of the left lung in the roentgenogram of the excised lungs was smaller than usual, and a V-shaped indentation in it suggested the presence of a scar in the lung. At necropsy there was a pin-head-sized gray focus, with a yellow centre, on the dorsal surface of the right upper lobe. There were some irregular grooves in the left lower lobe. A streak-like area of gray consolidation lay at the base of one of the grooves. Two of the paratracheal nodes were large, soft and gray. There were no macroscopic tuberculous lesions in the other viscera. A section through the lesion in the right upper lobe showed a subpleural tubercle with a soft necrotic core. The pleura overlying it showed signs of a chronic inflammatory process. A few alveoli about the tubercle contained mononuclear

leucocytes. Sections through the left lower lobe showed two areas of puckering. The more prominent of these presented the following features: Opposite a V-shaped recess in the lung there were some large bronchi surrounded by many lymphocytes. The interalveolar septa between the bronchi and the apex of the "V" were short and relatively thick. The intervening alveoli were small and very irregular in shape. The alveoli adjacent to this area were emphysematous. The pulmonary lymphoid tissue in this vicinity was hypertrophic and hyperplastic. A section stained for elastic tissue showed some thickening of the pleura in the area of puckering just described. It also demonstrated that there was an abundance of elastic tissue in the foreshortened and distorted interalveolar septa and in those overstretched as the result of emphysema. (The roentgenological and pathological findings of rabbit 317 are shown in plate V.)

Rabbit No. 314: Killed at 24¼ weeks: The shadows in the chest roentgenograms of this animal were comparable to those of the foregoing animals except in that they did not disappear until a slightly later date, as is shown in table 2. The films of the excised lungs failed to reveal any evidence of disease. At necropsy, however, a small area of pale gray consolidation was found in the apex of the left lower lobe. The lungs inflated readily in the negative-pressure chamber, but even at the height of inflation there were a few faint grooves in the site mentioned. The paratracheal lymph nodes were large, soft and gray. The other viscera contained no gross tuberculous lesions. The sections gave a picture similar to that described above. In this case, however, more of the alveoli bounded by distorted septa contained mononuclear leucocytes.

The chest roentgenograms of 2 rabbits, one killed in the 4th month and one killed in the 6th month, were negative. The roentgenogram of the excised lungs of the animal killed in the 4th month suggested the presence of disease in the left lung, for the outline of the left lung field was irregular. Necropsy examination showed in the left lower lobe two areas in which there were thick interalveolar septa, distorted alveoli, some of which contained mononuclear leucocytes, and a cluster of abnormally large bronchi surrounded by lymphocytes. Some of the alveoli in the vicinity of these lesions were emphysematous. The roentgenogram of the excised lungs of the animal killed in the 6th month failed to reveal any evidence of disease, yet there were macroscopic tuberculous lesions in the lungs.

Both the chest roentgenograms and the roentgenograms of the excised lungs of many of the rabbits, taken after the 6th month, contained no abnormal shadows. The postmortem findings showed that healing by

resolution had taken place in the majority of the animals killed after this time. The following protocol contains the roentgenological and pathological findings of a rabbit killed during the 8th month:

Rabbit No. 303: Killed at 31$\frac{2}{7}$ weeks: The shadows in the chest roentgenograms were comparable to those of rabbits killed at earlier periods. There were no abnormal shadows in the final chest films. Furthermore, there were no abnormal shadows in the films of the excised lungs. At necropsy the lungs appeared natural. They inflated uniformly in the negative-pressure box. The paratracheal lymph nodes, however, were moderately enlarged. They were soft and brown. There were no macroscopic tuberculous lesions in the other organs. Sections taken from various parts of the lungs contained no tubercles. The lymphoid tissue in the left lower lobe was hypertrophic and hyperplastic. (The roentgenological and pathological findings of rabbit 303 are illustrated in plate VI.)

An analysis of the roentgenological and pathological findings of the 12 rabbits killed between the 8th month and the 4th year showed the following interesting points: The final chest films of nine contained no abnormal shadows. The films of the excised lungs of seven of these were negative. Necropsy examination of the latter rabbits failed to disclose any trace of disease. The films of the excised lungs of two, however, contained abnormal shadows. In one instance the shadows were cast by minute areas of consolidation of undetermined aetiology; in the other, by miliary tubercles. Accordingly, although the final chest roentgenograms of three-quarters of the 12 rabbits were negative, postmortem examination showed that healing by resolution had occurred in slightly less than two-thirds of this number. The final chest roentgenograms of one-quarter of the 12 rabbits contained abnormal shadows. Necropsy examination disclosed fibrocaseous and fibrocalcareous lesions in the lungs of these rabbits.

Although the lesions of most of the rabbits followed more than 8 months healed by resolution, the lesions of a few, as noted above, failed to do so. The following case is interesting in that, although there were no abnormal shadows in chest roentgenograms taken after the 3rd month, a caseous paratracheal lymph node, miliary tubercles in the lungs, spleen and kidneys, and tuberculous lesions in the appendix were found at necropsy:

Rabbit No. 202: Killed at 74$\frac{6}{7}$ weeks: The chest film taken at 2$\frac{6}{7}$ weeks contained a small homogeneous shadow with an indefinite margin. The shadow was

larger at $4\frac{3}{7}$ weeks, and absent at $10\frac{3}{7}$ weeks. The last chest film, made at $74\frac{5}{7}$ weeks, was negative. The roentgenogram of the excised lungs, however, disclosed elliptical shadows adjacent to the outline of the trachea, and mottled shadows through both lung fields. A lipiodol study failed to show any gross abnormality of the bronchi. (The animal was killed because of diarrhoea and loss of weight.) Both lungs were studded with pin-point to pin-head-sized gray tubercles. There was a cluster of tubercles in one portion of the diaphragmatic border of the right lower lobe. The paratracheal lymph nodes were large, soft and gray. The terminal part of the appendix was the seat of a chronic tuberculous process. A large lymph node near the ileocaecal junction contained caseous material. There were tubercles in the kidneys and the spleen. The other organs presented no macroscopic evidence of tuberculosis. The sections confirmed the gross pathological findings. Some of the tubercles in the lungs contained caseous foci. One of the paratracheal lymph nodes had a caseous core. The lesions in the appendix were tuberculous. Acid-fast bacilli were found in the caseous paratracheal lymph node, the wall of the appendix, and some mucoid material taken from the lumen of the appendix.

In the foregoing instance the final chest roentgenograms contained no abnormal shadows. The roentgenograms of the excised lungs, however, contained elliptical shadows adjacent to the outline of the trachea and fine mottled shadows throughout both lung fields. The former were cast by large paratracheal lymph nodes; the latter, by miliary tubercles. The original lesions in the left lung apparently healed, leaving a caseous focus in a paratracheal lymph node. Subsequently tubercle bacilli escaped, presumably from the lymph node, and caused miliary tuberculosis.

It may be well to note at this point that, although the chest roentgenograms regularly failed to reveal evidence of large paratracheal lymph nodes, the roentgenograms of the excised lungs of practically all of the rabbits disclosed abnormal oval shadows near the outline of the trachea. These shadows, described in the protocols of the rabbits killed before the 10th day, were not mentioned when the roentgenological findings of rabbits killed between the 10th day and 8th month were presented. The shadows, with the exception of those in the films of rabbits 26 and 202, were cast by hypertrophic and hyperplastic lymph nodes. The paratracheal lymph nodes of the two animals mentioned contained macroscopic necrotic or caseous foci.

It is interesting that the chest roentgenograms of only a few rabbits contained signs of pulmonary cavities and that cavities were rarely

found at necropsy. The following protocols give the roentgenological and pathological findings of two rabbits which had cavities:

Rabbit No. 1: Killed at 10$\frac{4}{7}$ weeks: The chest roentgenogram taken on the 9th day disclosed a homogeneous shadow with indefinite margins in the left lung field. At 4$\frac{3}{7}$ weeks the shadow contained one area of rarefaction; and at 6 weeks, several areas of rarefaction. During the 6th week a new homogeneous shadow was detected in the right lung field. The shadows in both lung fields gradually increased in size, attaining greatest proportions the day the animal was killed. The roentgenogram of the excised lungs revealed extensive homogeneous shadows with multiple areas of rarefaction in the left lung field, and homogeneous shadows in the upper half of the right lung field. The left lung, as seen at necropsy, consisted of fibrocaseous lesions and cavities of various sizes. Both the visceral and parietal pleurae showed acute and chronic inflammatory changes. The right upper and middle lobes were red to gray in color and firm to touch. The sections confirmed the gross findings in the left lung and showed that the lesions in the right lung were tuberculous. The latter contained several large and poorly-walled-off caseous foci.

Rabbit No. 4: Killed at 4 years: The shadows in the early chest roentgenograms were comparable to those of the foregoing animal. Signs of cavity were first noted in the film made at 5 weeks. The shadows began to recede during the 3rd month, and the signs of cavity disappeared soon afterward. There were no abnormal shadows in the films taken at the end of the 1st year. About the middle of the 2nd year a faint homogeneous shadow containing some minute unusually dense shadows was detected in the chest films. The homogeneous shadow gradually disappeared. The minute dense shadows persisted. They slowly became more dense and more clearly defined. The location and character suggested calcified lesions in the left lower lobe. No new shadows were found in the chest roentgenograms until shortly before the rabbit was killed. At this time a small dense shadow was observed in the lower right lung field. (The animal was killed because it refused to eat and was becoming increasingly weak.) The films of the excised lungs contained an oval homogeneous shadow near the outline of the trachea, dense discrete shadows in the midportion of the left lung field, and scattered homogeneous shadows in the lower halves of both lung fields. There were three yellow masses of small size in the right pleural cavity. Delicate adhesions bound the left lower lobe to the chest-wall and the diaphragm. The left lower lobe was slightly smaller than usual. The apex was puckered. On cut-surface it showed several large bronchi and a small cavity. The walls of the latter contained calcareous material. There were also scattered areas of gray consolidation of varied size and shape in both the left and the right lungs. The right paratracheal lymph nodes were very large.

The liver, spleen, kidneys and adrenals contained no macroscopic tubercles. Sections taken from the apex of the left lower lobe showed a number of large bronchi, a healed cavity 1.5 mm. in diameter, several calcareous deposits, some fibrous tissue and many emphysematous alveoli. Strands of fibrous tissue surrounded the bronchi and partially encircled the cavity. In the fibrous tissue between the main bronchus and the cavity there were many calcareous foci. One of the latter bulged into the wall of the cavity. The cavity was lined with cuboidal epithelium. The alveoli adjoining these lesions were very large. Other sections showed areas of recent tuberculous pneumonia in both lungs. One large paratracheal lymph node contained many mononuclear leucocytes; another, a caseous focus and some giant cells. (Some of the roentgenograms of rabbit 4 have been reproduced in plate VII.)

Signs of cavity were detected in the chest roentgenograms of the above cases at the end of the 1st month. The later chest roentgenograms of the first rabbit revealed evidence of increasing cavity-formation and extension of the disease. The rabbit died during the 3rd month. The necropsy findings confirmed the roentgenological findings. The signs of cavity in the films of the second rabbit gradually disappeared and were not observed again during the period of the experiment. Roentgenograms taken during the 2nd year revealed discrete dense shadows where there had once been signs of cavity. These shadows, indicative of calcification, were a constant feature of all the films taken during the 3rd and 4th years. Abnormal shadows in the right lung field were first detected in films made shortly before the animal was killed. The roentgenograms of the excised lungs contained evidence of calcified areas in the left lower lobe and of numerous airless areas in both lungs. They failed, however, to reveal abnormal bronchi, a healed cavity, much fibrous tissue and many emphysematous alveoli in the left lower lobe.

An analysis of the roentgenological and pathological findings of all of the rabbits brought out the following interesting points concerning cavities: Signs of cavity were not detected in any of the chest roentgenograms taken before the end of the 1st month. The lungs of rabbits killed prior to this time contained no cavities. Signs of cavity were detected in the chest roentgenograms of only four of the 35 rabbits killed between the end of the 1st month and the 4th year. Necropsy examination showed that there were cavities in the lungs of these 4 animals and one other animal. The disease in four of the 5 animals with cavities extended to new areas in the lungs.

Finally, the shadows in the chest roentgenograms of one rabbit receded more slowly than those of the majority of the animals, became very dense

during the 2nd year and changed little afterward. The final roentgenological picture suggested a cluster of calcified tubercles in the left lower lobe. The roentgenological and pathological findings of this rabbit were as follows:

Rabbit No. 2: Killed at 3 years: The abnormal shadows in the chest roentgenograms attained greatest size at the 5th week and began to recede during the 3rd month. By the end of the 1st year the shadows consisted of a band, approximately 2 mm. wide, extending from the cardiac shadow to the outline of the left chest-wall, and containing one unusually dense area. During the 2nd year the band-shadow gave place to linear and isolated discrete shadows. The shadows in films taken in the 3rd year showed no appreciable change. The films of the excised lungs were noteworthy. The right lung field, which was very large, contained one small dense discrete shadow. The outline of the upper left lung field was indistinct; of the lower left lung field, small and irregular. The lower left lung field contained a cluster of small discrete dense shadows and a large homogeneous shadow with an area of rarefaction. The latter was situated in the extreme basal part of the lung field. The necropsy findings were as follows: Adhesions bound the left lower lobe to the lateral chest-wall. This lobe, which was small and wrinkled, showed on cut-surface large distorted bronchi, several calcareous deposits, areas of fibrosis and emphysema, and at the extreme base a recent area of caseous pneumonia with a small cavity. The left upper lobe and the right lung were very large. Two of the paratracheal lymph nodes were large, soft and gray; one was small and firm. The other viscera contained no macroscopic tuberculous lesions. The sections confirmed the gross necropsy findings. There was an isolated fibrocalcareous lesion in the right lung. The alveoli of the left upper lobe were two to three times the usual size. The striking features of the left lower lobe were a large distorted bronchus with thick fibrous walls containing isolated calcareous deposits and an area of caseous pneumonia with a cavity. The walls of the large bronchus were lined in part with cuboidal epithelium. Adjacent to the bronchus there were several small irregularly-shaped bronchi containing cellular debris. Strands of fibrous tissue infiltrated with lymphocytes surrounded the bronchi and radiated in all directions. In some of the strands of fibrous tissue, particularly those near the interlobar surface, there were isolated caseous tubercles. The visceral pleura in the vicinity of these tubercles contained many dilated lymph channels and much fibrous tissue. Among the abnormal bronchi and the strands of fibrous tissue there were small groups of emphysematous alveoli, a few of which contained mononuclear leucocytes. The area of caseous pneumonia at the base of the lung showed no signs of healing. (The essential roentgenological and pathological findings of rabbit 2 are illustrated in plates VIII & IX.)

The serial chest roentgenograms described in the above protocol pointed to healing of an extensive lesion by fibrosis and calcification. The films of the excised lungs disclosed additional information concerning the location and the nature of the lesions. They revealed a small left lower lobe containing several calcareous deposits and an area of consolidation with a cavity, an emphysematous left upper lobe and a large right lung containing an isolated fibrocalcareous lesion. A comparison of the discrete shadows in the films of the excised lungs and the films of the lungs *in situ* showed that there was an isolated shadow, comparabe to the one in the right lung field of the former, in the left lung field of the latter.

Examination of the lungs at necropsy disclosed many lesions that the chest roentgenograms failed to reveal. The examination also showed certain important features of the lesions and the surrounding tissues that were not revealed by the roentgenograms of the excised lungs. The left lower lobe, which was small, contained distorted bronchi surrounded by fibrous tissue in which there were isolated calcareous deposits, areas of compensatory emphysema, and an area of recent tuberculous pneumonia with cavity. The left upper lobe was markedly emphysematous. The right lung, which showed signs of hypertrophy, contained one small fibrocalcareous lesion.

DISCUSSION AND SUMMARY

Primary experimental pulmonary tuberculosis, comparable in many ways to pulmonary tuberculosis in children, has been produced in rabbits by the intratracheal injection of measured quantities of tubercle bacilli.

The rabbits, like many children with pulmonary tuberculosis, did not appear ill. They ate well and grew as rapidly as healthy control animals. They had no fever during the early progressive phases of the disease.

The first chest roentgenograms of the rabbits, in which abnormal shadows were detected, were those taken between the 10th and 17th days. Films taken during the 2nd month usually contained the largest abnormal shadows. Films made in the 3rd and 4th months commonly contained fewer and smaller shadows. In some instances no abnormal shadows were detected in chest roentgenograms taken after the 3rd month. In other instances the shadows in successive chest roentgenograms gradually became dense and discrete and, having attained this status, changed little during a period of years. Stereoscopic roentgenograms of the excised lungs invariably contained more abnormal shadows

han the chest roentgenograms. Comparison of the roentgenological and athological findings showed that the roentgenograms of the excised ungs yielded more information with respect to the location and size of he pulmonary lesions than the roentgenograms made during life. The oentgenograms of the excised lungs, like the chest roentgenograms, failed n many instances to portray the nature of the disease.

The lesions of rabbits killed at successive stages showed the gradual levelopment of tubercles, the coalescence of tubercles to form pneumonic areas, and the development in the latter of necrotic and caseous foci. The caseous areas, unlike those in the lesions of rabbits with reinfection experimental pulmonary tuberculosis to be described in the subsequent paper, were small. Some of them contained stainable elastic tissue in alveolar arrangement. The lungs of rabbits killed at later periods demonstrated for the first time in a striking manner successive stages in the healing of primary pulmonary tuberculosis. They showed various phases in the healing of tubercles and large areas of tuberculous pneumonia by resolution. The fact that the lungs and paratracheal lymph nodes of 7 of the 12 rabbits killed between the 8th month and the 4th year presented no residual evidence of disease is significant. Moreover the lungs of some of the rabbits showed various stages in the healing of tuberculous lesions by resolution, fibrosis and calcification and, in addition, certain compensatory phenomena such as emphysema and abnormalities of the bronchi. The lungs of the rabbits killed at the end of the 3rd and the 4th years contained calcified tubercles, small fibrocaseous lesions, cavities, abnormal bronchi and areas of compensatory emphysema. The fact that cavities were found in the lungs of only five of the 35 animals killed between the end of the 1st month and the end of the 4th year is significant. Although the paratracheal lymph nodes of all of the rabbits were large and some contained caseous foci, none presented evidence of calcification. Otherwise primary experimental pulmonary tuberculosis produced in rabbits by the intratracheal injection of measured quantities of tubercle bacilli is strikingly similar both roentgenologically and pathologically to pulmonary tuberculosis in children.

REFERENCES

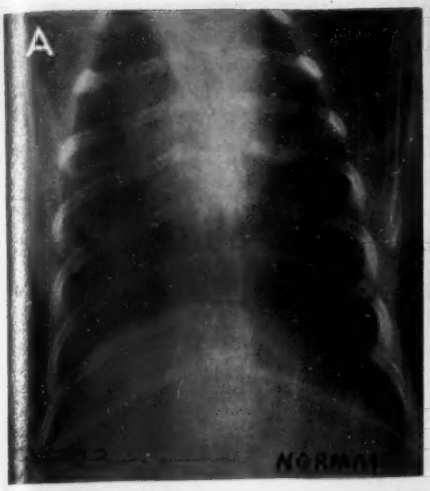
BALDWIN, E. R., AND GARDNER, L. U: Amer. Rev. Tuberc., 1921, v, 429.
BURKE, H. E.: (In press.)
CORPER, H. J.: Amer. Rev. Tuberc., 1922, vi, 851.
GREENBERG, S.: Ibid., 1933, xxvii, 137.
LEWIS, P. A., AND MONTGOMERY, C. M.: J. Exper. Med., 1913, xvii, 527.

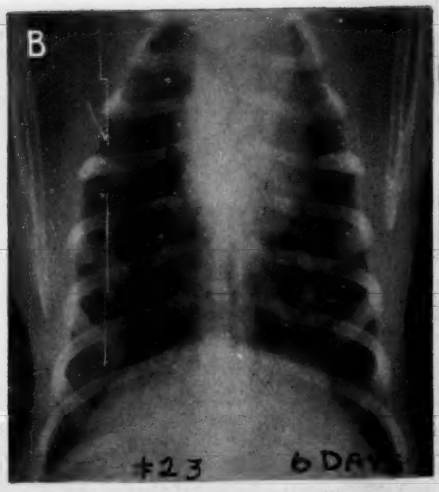
MULLIN, W. V., AND RYDER, C. T.: Amer. Rev. Tuberc., 1920, iv, 683.
PRUDDEN, T. M.: New York M. J., 1894, lx, 1.
ROGERS, J. B.: Amer. Rev. Tuberc., 1920, iii, 750.
SOPER, W. B., SAMPSON, H. L., AN HASKINS, C. H.: Ibid., 1927, xv, 88.

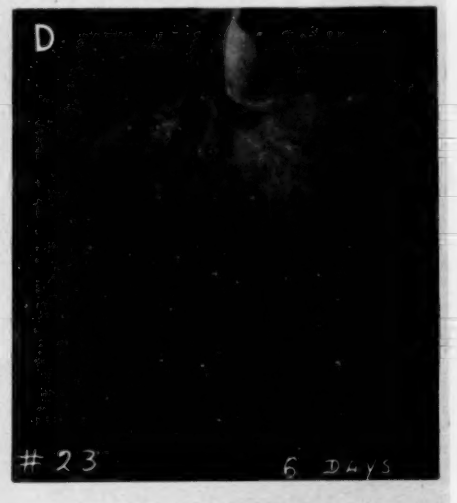
PLATE I

Rabbit 23

A. P. A. film before injection. No abnormal shadows.
B. P. A. film 6 days after injection. No abnormal shadows.
C. Lateral film. No abnormal shadows.
D. Film of excised lungs. Abnormal shadow cast by lymph node.
E. Photograph of section showing large paratracheal lymph node.
F. Interalveolar mononuclear leucocyte containing tubercle bacilli. ×1350.







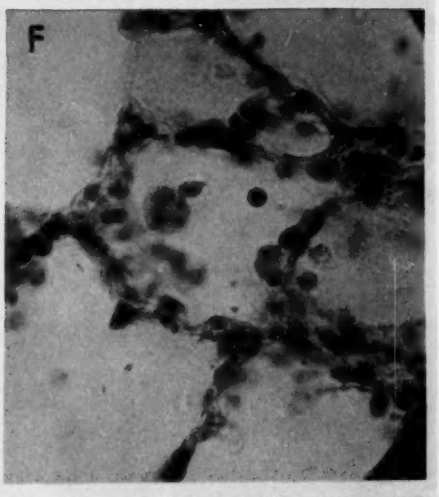


PLATE I

RABBIT NO. 23

PLATE II

Rabbit 26

A. P. A. film at 12 days. Abnormal shadows left lung field.

B. Lateral film. No abnormal shadows.

C. Film of excised lungs. Extensive shadows.

D. Photograph of section. Macroscopic tubercles and lymph node.

E. Isolated and clustered tubercles. ×6.

F. An early tubercle. ×120.

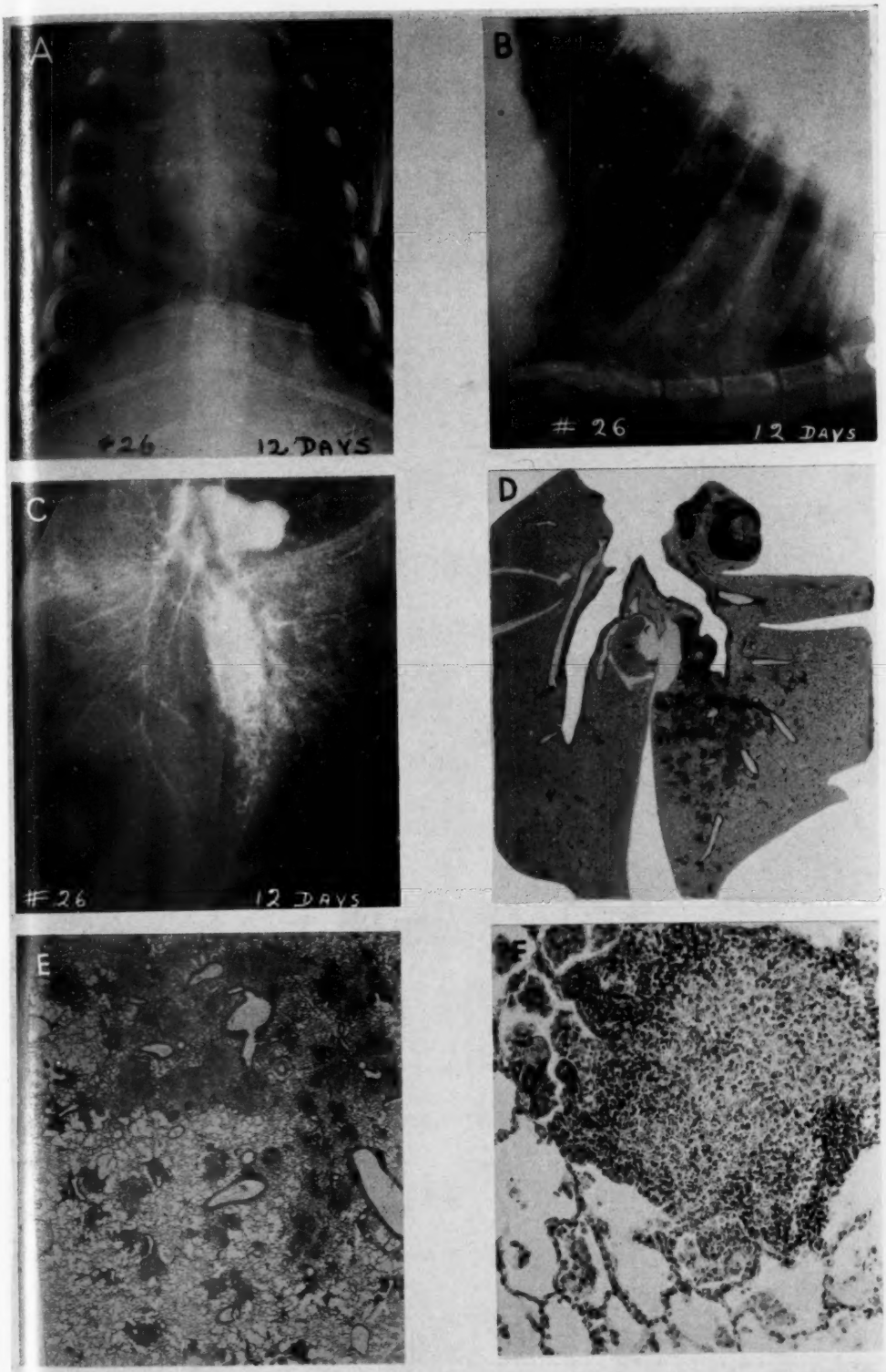


PLATE II RABBIT NO. 26

PLATE III

Rabbit 331

A. Film at 12 days. Abnormal shadows, left lung field.

B. Film at $3\frac{1}{7}$ weeks. Large abnormal shadows, left lung field.

C. Film of excised lungs. Homogeneous shadow with definite and indefinite margins.

D. Photo of section showing areas of tuberculous pneumonia.

E. Necrotic and caseous foci in a pneumonic area. ×6.

F. Periphery of a caseous focus in a pneumonic area. ×120.

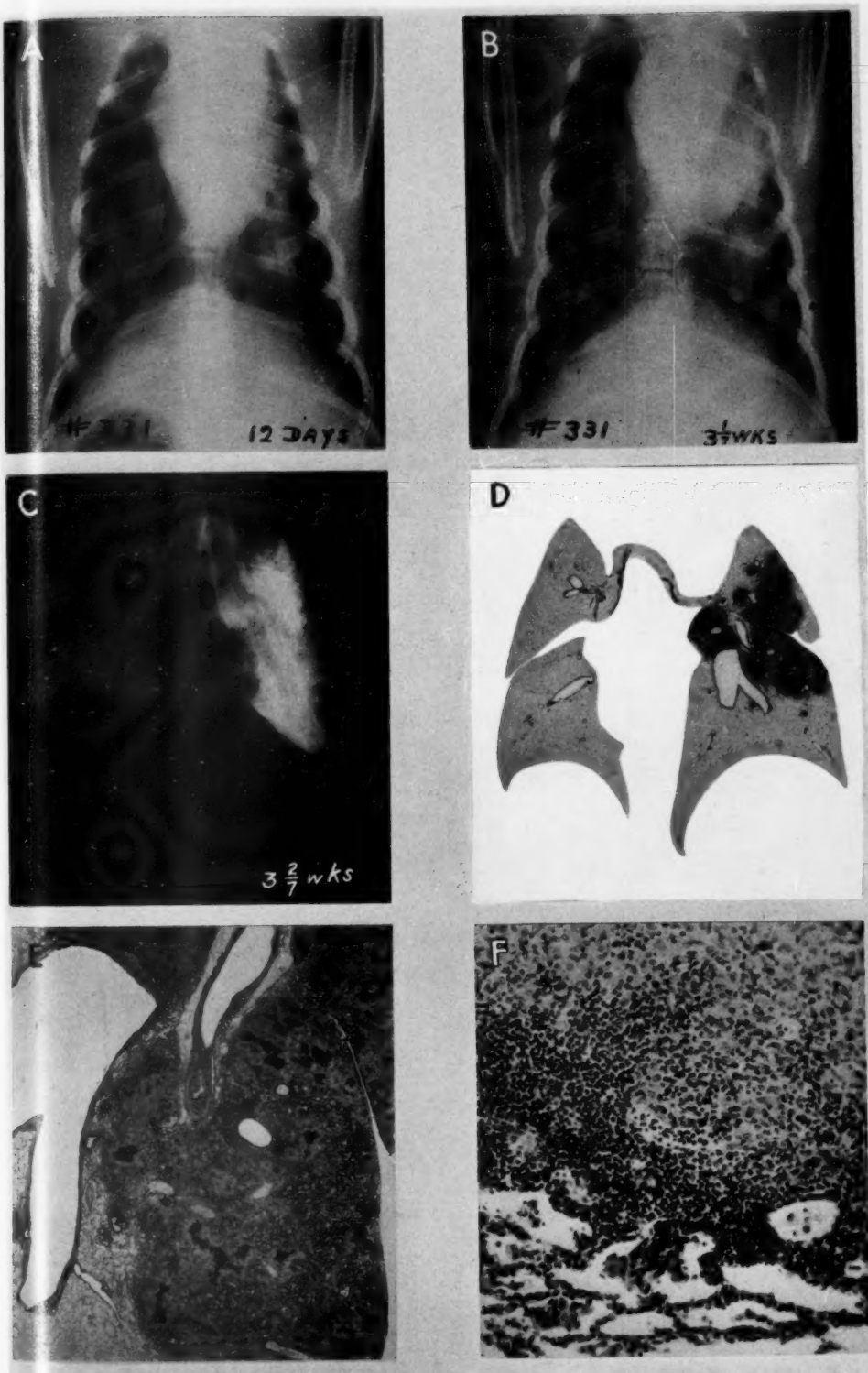


PLATE III

RABBIT NO. 331

PLATE IV

Rabbit 323

A. Film at $4\frac{2}{7}$ weeks. Large homogeneous shadow with indefinite margins.

B. Film at 2 months. Mottled shadows occupying small part of left lung field.

C. Film of excised lungs. Mottled shadows left lung field.

D. Photograph of section, showing lesions of varied size in left lung.

E. Isolated and clustered tubercles. ×6.

F. Lymphocytes and fibroblasts in the periphery of a tubercle. ×120.

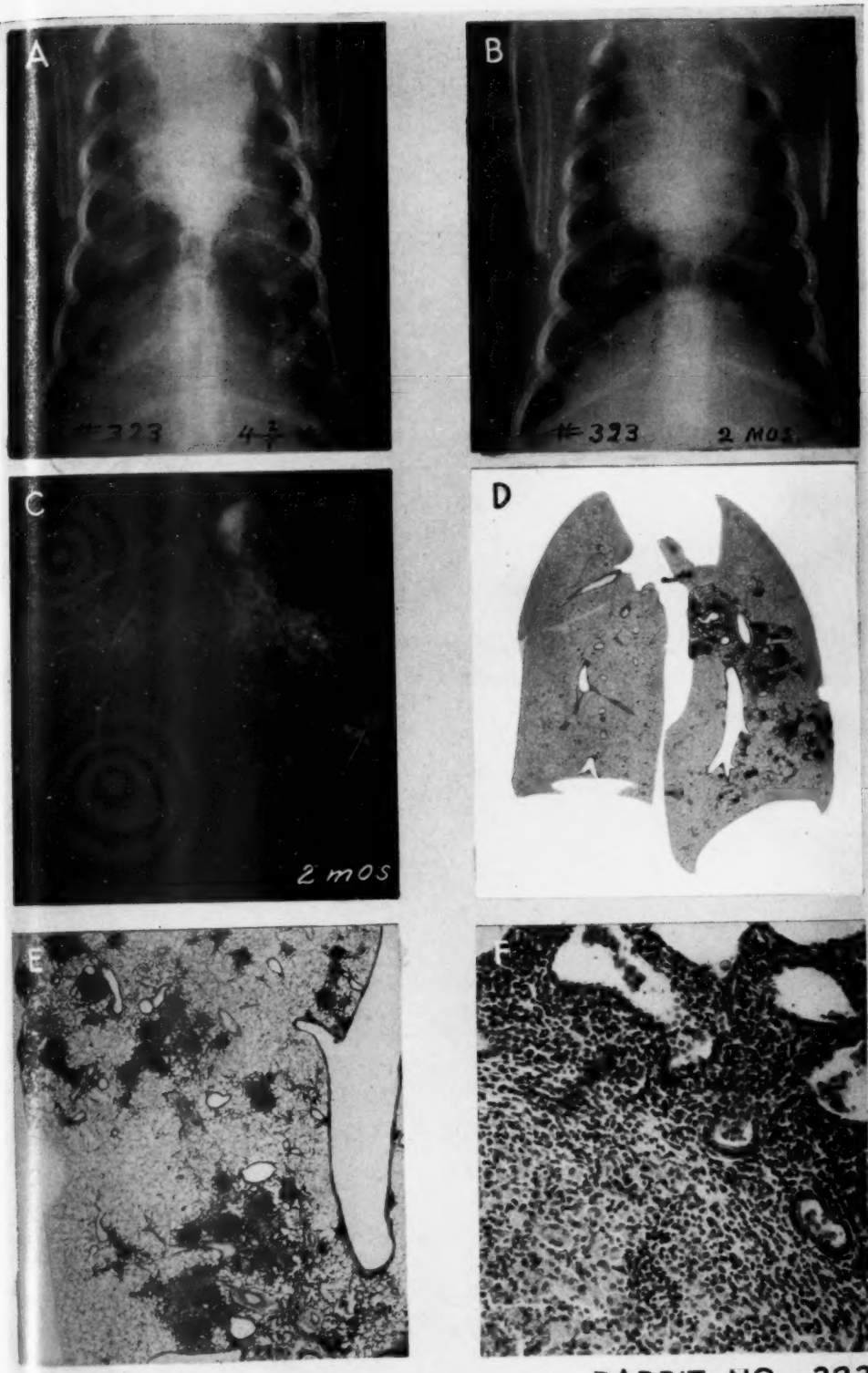


PLATE IV

RABBIT NO. 323

PLATE V

Rabbit 317

A. Film at $2\frac{1}{7}$ weeks. Abnormal shadows left lung field.

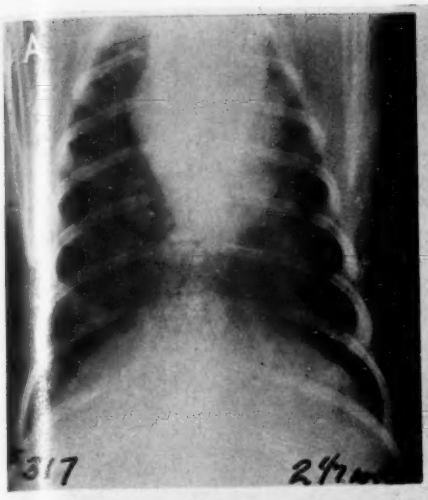
B. Film at $5\frac{1}{7}$ weeks. Abnormal shadows, left lung field.

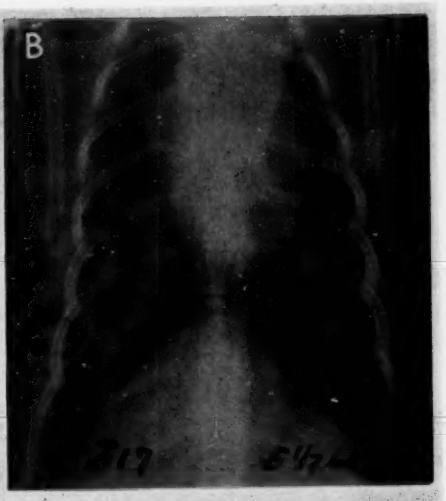
C. Film at $17\frac{5}{7}$ weeks. No abnormal shadows.

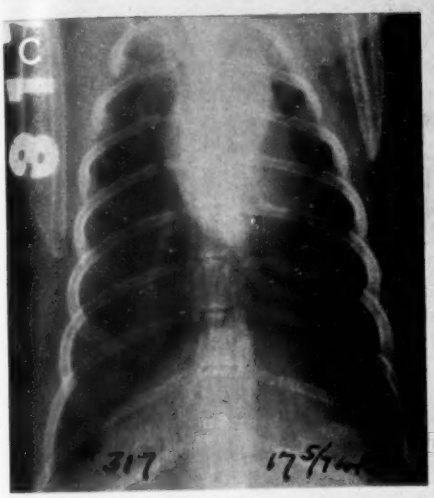
D. Film of excised lungs. Left lung field smaller than right lung field.

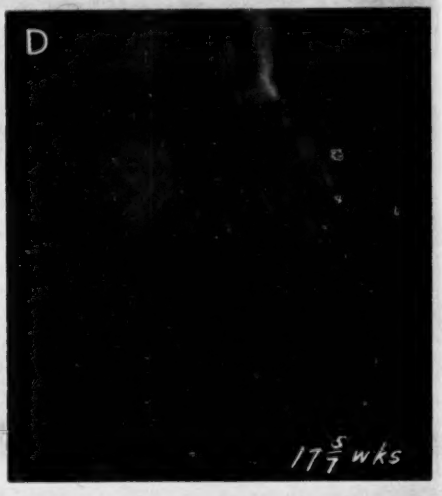
E. Photograph of section. Area of puckering in left lung.

F. Distorted alveoli in area of puckering. Elastic tissue stain. ×60.









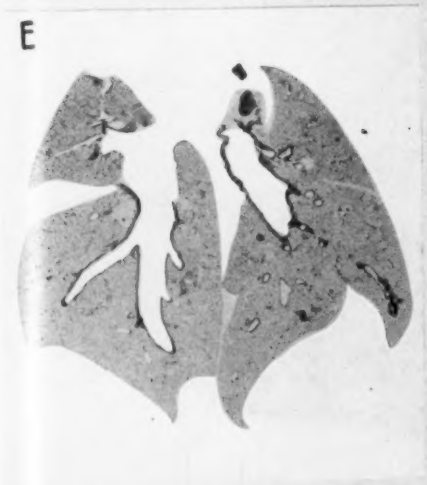


PLATE V

RABBIT NO. 317

PLATE VI

Rabbit 303

A. P. A. film at $2\frac{1}{7}$ weeks. Abnormal shadows, left lung field.

B. P. A. film at $31\frac{2}{7}$ weeks. No abnormal shadows.

C. Lateral film at $31\frac{2}{7}$ weeks. No abnormal shadows.

D. Film of excised lungs. Only abnormal shadows cast by paratracheal nodes.

E. Photograph of section. No macroscopic lesions.

F. Portion of left lower lobe. Only hyperplastic lymphoid tissue. ×100.

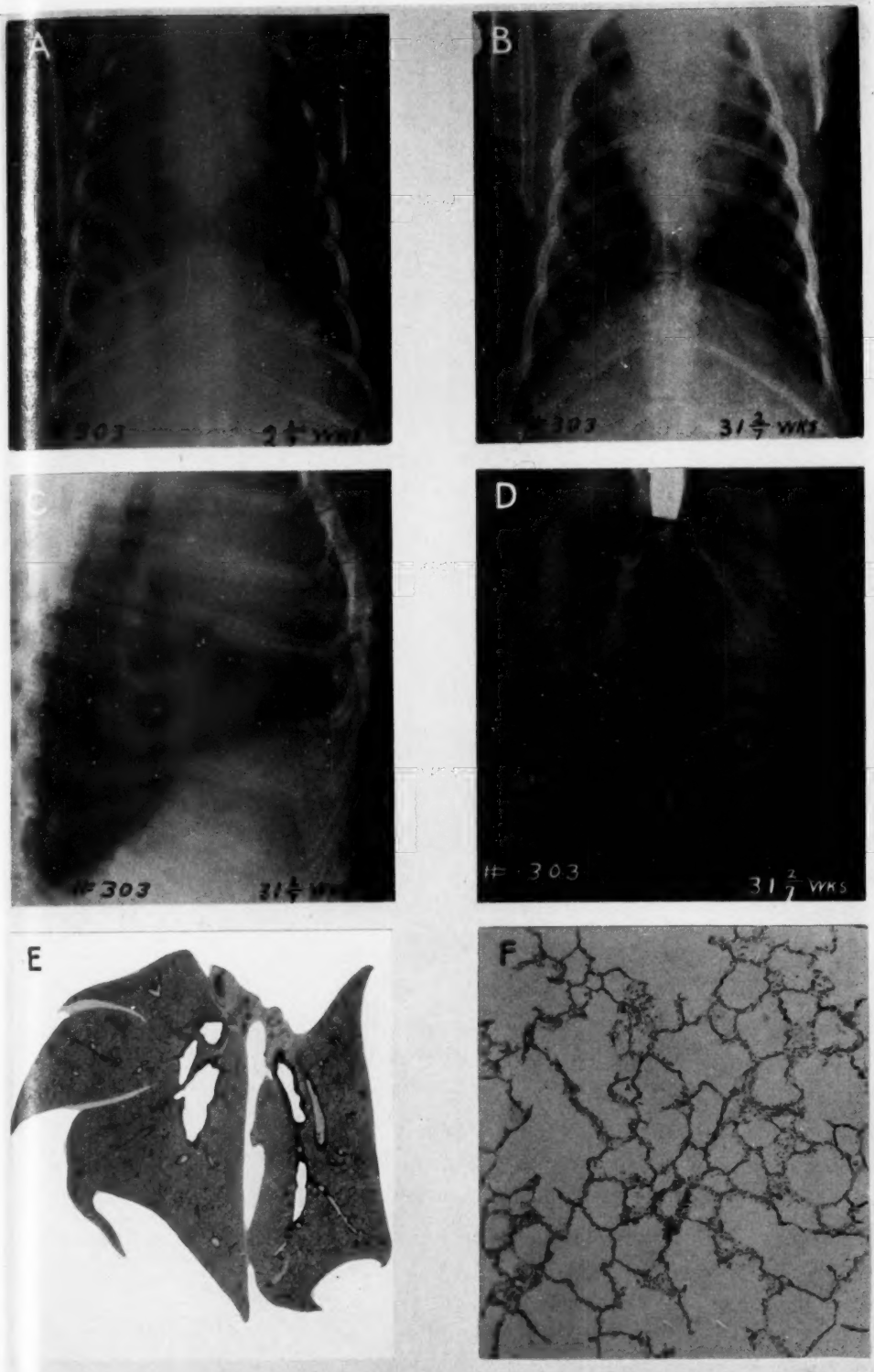


PLATE VI

RABBIT NO. 303

PLATE VII

Rabbit 4

A. Film at 17 days. Abnormal shadow, left lung field.

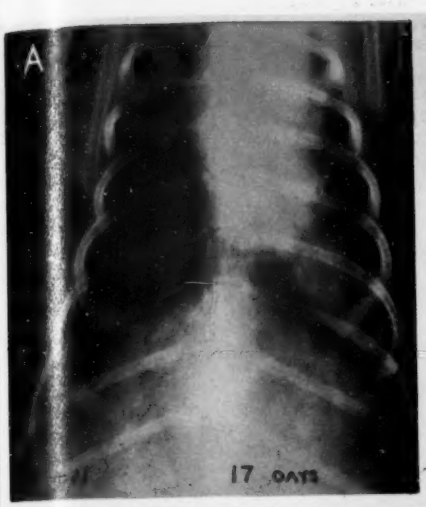
B. Film at 5 weeks. Extensive shadow with signs of cavity.

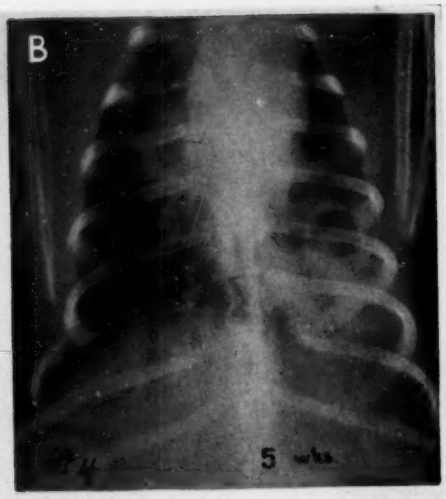
C. Film at $12\frac{4}{7}$ weeks. Shadow smaller. Signs of cavity indistinct.

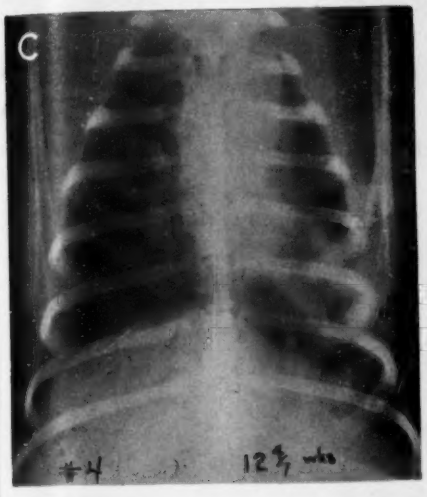
D. Film at $79\frac{3}{7}$ weeks. Minute discrete shadows and faint homogeneous shadow.

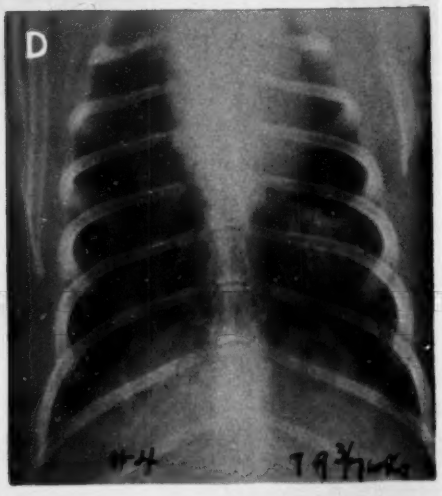
E. Film at 4 years. Dense discrete shadows, left lung field and also right lung field.

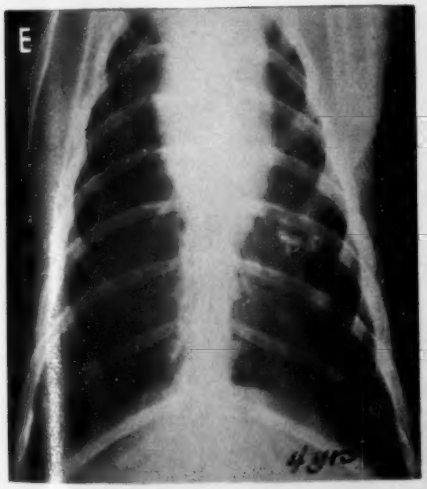
F. Film of excised lungs. Shadows cast by large lymph nodes, calcified lesions in left lung and areas of consolidation in lower halves of both lungs.











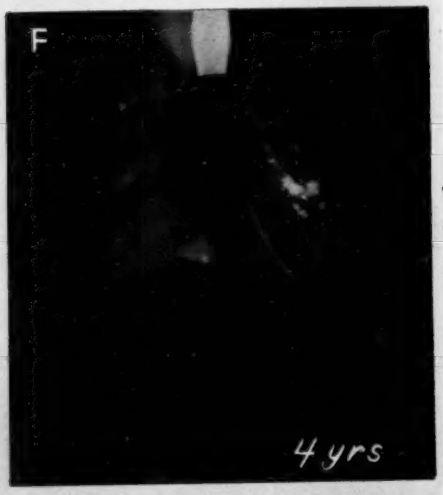


PLATE VII

RABBIT NO. 4

PLATE VIII

Rabbit 2

A. Film at $9\frac{4}{7}$ weeks. Extensive shadows left lung field.

B. Film at $23\frac{1}{7}$ weeks. Shadows much smaller.

C. Film at $43\frac{3}{7}$ weeks. Band shadow.

D. Film at $101\frac{3}{7}$ weeks. Dense discrete shadow and linear shadow.

E. P. A. film at 3 years, $4\frac{2}{7}$ weeks, similar to *D*.

F. Lateral film at 3 years, $4\frac{2}{7}$ weeks. Dense discrete shadows.

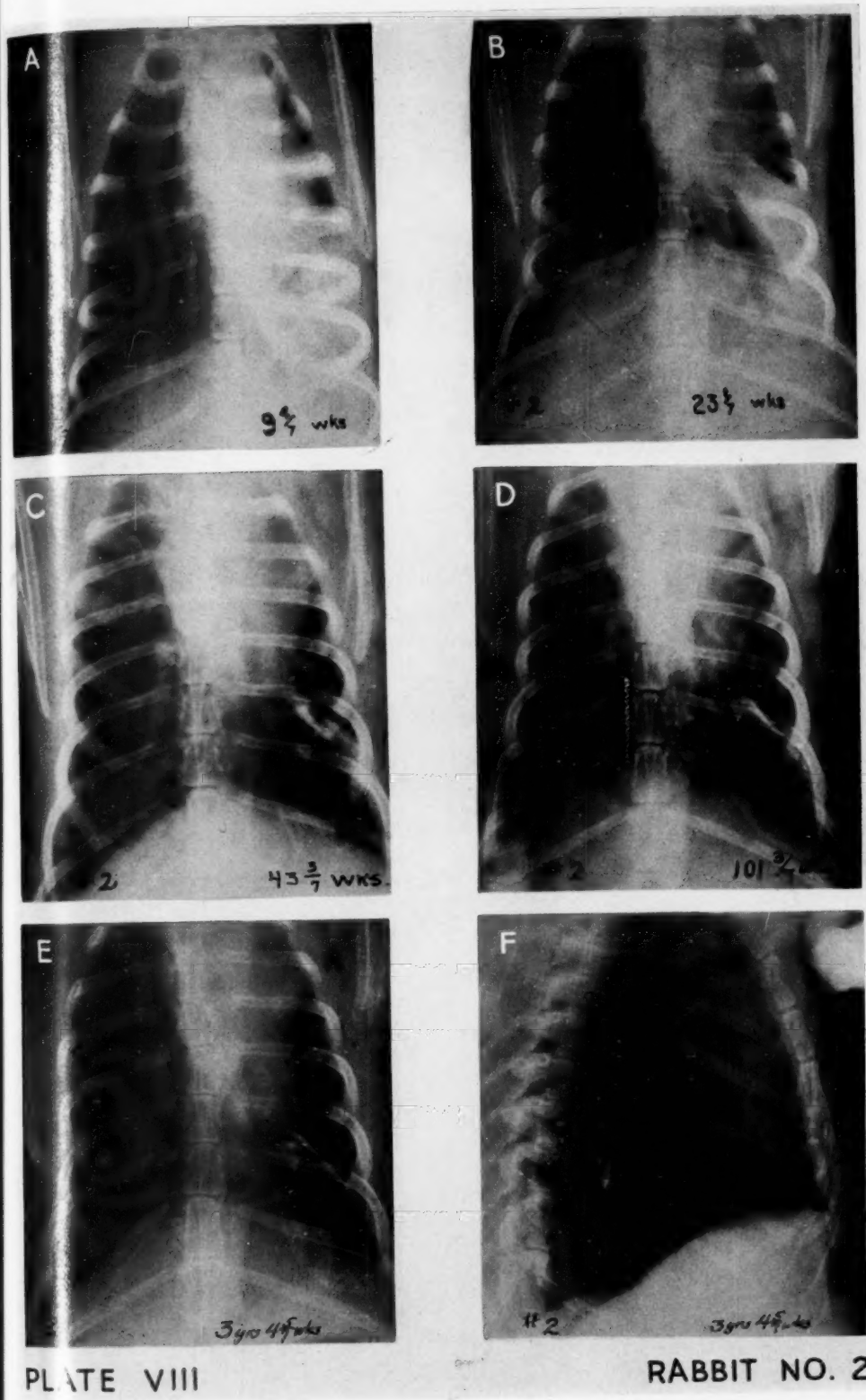


PLATE VIII

RABBIT NO. 2

PLATE IX

Rabbit 2.

A. Photograph showing adhesions binding left lung to chest-wall.

B. Film of excised lungs. Large right lung field with isolated discrete shadow. Small left lung field with dense discrete shadows, and homogeneous shadow with signs of cavity.

C. Photograph of section. Large right lung. Emphysematous left upper lobe and diseased left lower lobe.

D. Portion of left lower lobe. Abnormal bronchi, tubercles, fibrosis and compensatory emphysema. ×15.

E. Thickened pleura and area of compensatory emphysema. Elastic-tissue stain. ×60.

F. Tubercle near point of origin of an adhesion. ×60.

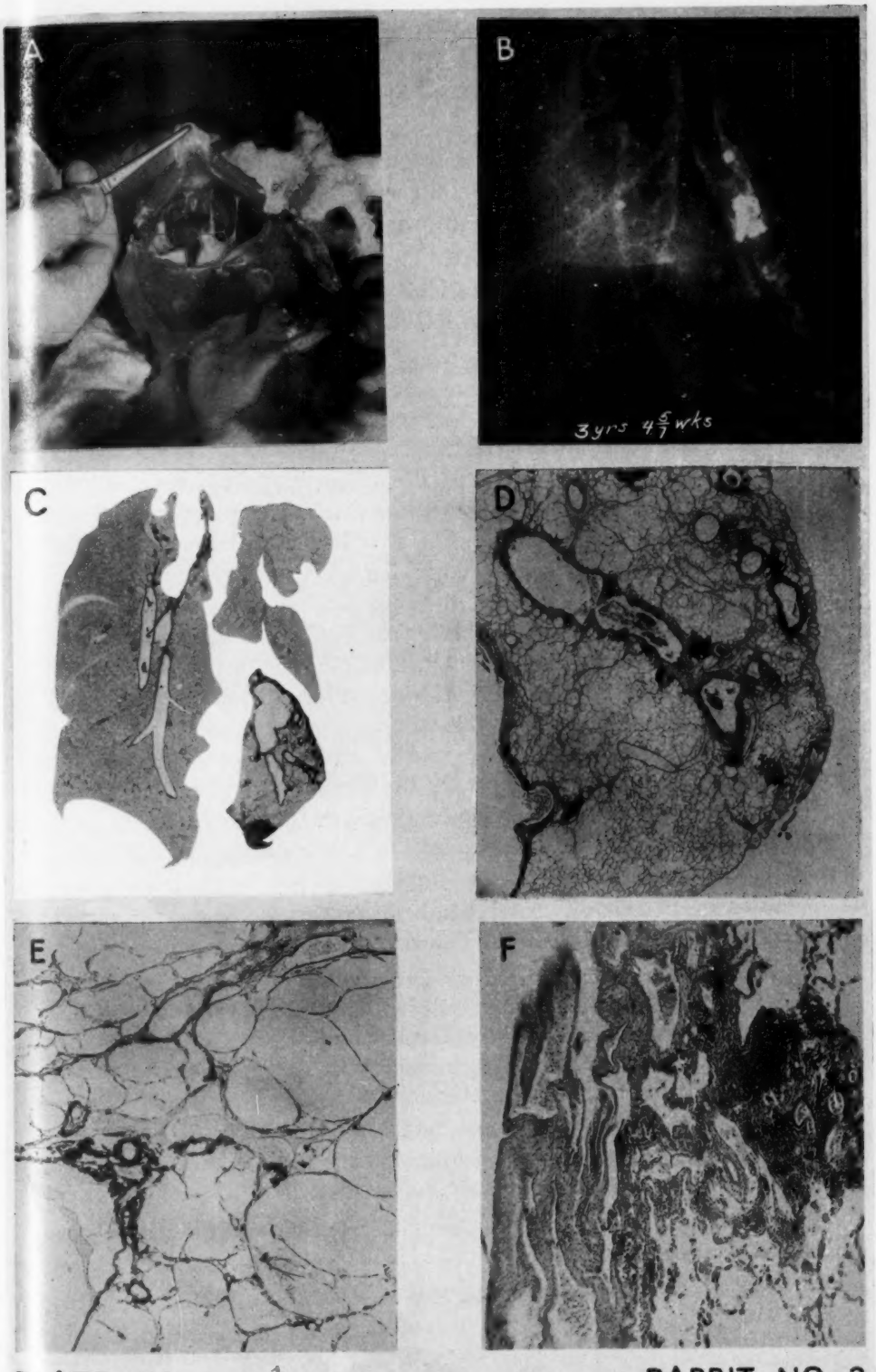


PLATE IX

RABBIT NO. 2

A COMPARISON OF THE ROENTGENOLOGICAL AND PATHOLOGICAL FINDINGS IN EXPERIMENTAL PULMONARY TUBERCULOSIS IN RABBITS[1]

PART 2. Reinfection Tuberculosis

HUGH E. BURKE

When rabbits with a tuberculous focus in the groin are injected intratracheally with measured quantities of tubercle bacilli, lesions develop which are different in some respects from those of primary experimental pulmonary tuberculosis. These reinfection lesions are comparable roentgenologically and pathologically to retrogressive pulmonary tuberculosis in adult man.

The roentgenological and pathological findings of rabbits having a localized tuberculous lesion in the groin at the time of the intratracheal injection of a measured quantity of virulent human tubercle bacilli will be presented and discussed in this paper.

REINFECTION EXPERIMENTAL PULMONARY TUBERCULOSIS

Experimental

Rabbits: The rabbits were litter mates of those used in the study of primary experimental pulmonary tuberculosis. They were kept in cages indoors and given a mash containing ground oats, bran, linseed meal and skimmed-milk powder as well as liberal quantities of raw carrots and cabbage.

Subcutaneous injections: Each of the animals was inoculated in the groin with 0.5 to 1.0 cc. of a heavy suspension of avirulent tubercle bacilli,[2] cultivated on synthetic broth of pH. 7^1–7^4, approximately 3 weeks prior to the intratracheal injection of virulent tubercle bacilli. No attempt was made to measure the quantity of avirulent organisms accurately.

Intratracheal injections: The rabbits were injected intratracheally with 1 mgm. of virulent human tubercle bacilli,[2] the technique employed being that described in the first part of this study.

Roentgenograms were made at frequent intervals and autopsies were performed at selected times, as also described in the first part.

[1] From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

[2] Strain R1, Saranac Laboratory.

Before presenting the roentgenological and pathological findings in these rabbits it may be well to give a brief statement concerning the observations of other investigators who have studied reinfection experimental pulmonary tuberculosis.

In 1921 Baldwin and Gardner published an essay on reinfection tuberculosis in which they reviewed the literature, gave the results of their experimental studies and attempted to correlate the latter with various clinical observations. They employed guinea pigs, infecting the animals by the inhalation of a spray containing avirulent bacilli and, after the lapse of a year or more, reinfecting them by inhalation of sprays containing either avirulent or virulent bacilli. The data obtained in this study were not sufficient to permit the authors to describe in detail the pathogenesis of reinfection pulmonary tuberculosis. In 1925 Philibert and Cordey produced reinfection pulmonary tuberculosis in rabbits by the injection of both human and bovine tubercle bacilli. They injected some of their rabbits subcutaneously and then intratracheally, some intratracheally and then intravenously, and some intratracheally on two different occasions. Pulmonary lesions, similar to those to be reported in the present paper, developed in the rabbits injected intratracheally. Soper, Sampson and Haskins (1927) appear to be the only workers who have made a roentgenological study of reinfection experimental pulmonary tuberculosis. They used rabbits, instilling heavy suspensions of bovine bacilli into the nares of the animals and allowing them to aspirate the bacilli into the lungs. Most of the rabbits had progressive pulmonary lesions.

Fifty-eight rabbits were employed in the present study. All of the animals were injected in the groin with a suspension of avirulent tubercle bacilli several weeks prior to the intratracheal injection and most of them had a palpable cold abscess in the groin at the time of the intratracheal injection. All were injected intratracheally with 1 mgm. of virulent human tubercle bacilli.[3] Efforts to localize the bacilli in the left lung were successful, as the data in table 1 indicate. The rabbits were handled in small groups. The results were sufficiently uniform to warrant the construction of a composite roentgenological and pathological picture of reinfection experimental pulmonary tuberculosis.

The chest roentgenograms of the reinfected rabbits, taken at the end of the 1st day following the intratracheal injection, invariably contained abnormal shadows, as the data in table 1 indicate. The contrast between the roentgenological findings of the rabbits with reinfection tuberculosis and those with primary tuberculosis, described in the preceding paper, is striking. The essential roentgenological and pathological findings of a rabbit killed on the 1st day are as follows:

Rabbit No. 73: Killed on the 1st day: An abnormal homogeneous shadow was detected in the left lower lung field of a chest roentgenogram taken at the end of the 1st day. The films of the excised lungs showed a large homogeneous

[3] Strain H37, Saranac Laboratory.

shadow of irregular shape in the left lung field and elliptical shadows near the outline of the trachea. They proved to depict the site and size of the disease better than the chest film. Inspection of the lungs disclosed large areas of dull red consolidation in the medial and dorsal portions of both the left upper and the left lower lobes. These areas did not inflate as well as the other parts

TABLE 1

CASE NUMBERS	NUMBER OF RABBITS	LUNG SUPPOSEDLY INOCULATED	FIRST ABNORMAL SHADOW IN CHEST ROENTGENOGRAM	SITE AND CERTAIN SPECIAL FEATURES OF DISEASE	DURATION OF EXPERIMENT
					days
39–48		Left	1st day	Left lung	
A	6				2–8
B	See table 2				
72–79	8	Left	1st day	Left lung	1–12
80–88		Left	1st day	Left lung	
A	6				1–39
B	See table 2				
121–129		Left	1st day		
A	4				
121				Left lung	10
126				Left lung	12
123				Left lung; cavity	14
124				Both lungs; miliary	15
B	See table 2				
271–278	8	Left	1st day		
274				Left lung	1
272				Left lung	2
275				Left lung	4
277				Left lung	6
273				Left lung; empyema	8
276				Left lung	8
278				Left lung	10
271				Left lung	12

of the lungs. The paratracheal lymph nodes were slightly enlarged. There were cold abscesses in the groin and the external iliac nodes were somewhat larger than usual but contained no caseous foci. The other organs presented no gross evidence of tuberculosis. Sections through the left lung showed extensive pneumonic areas adjacent to the large bronchi. The alveoli in these areas were filled with cellular exudate and amorphous debris. The exudate

consisted of mononuclear leucocytes and traces of fibrin. In some parts of the consolidated areas the septa were thick and contained dilated capillaries. In other parts they could not be identified. Many of the small bronchi in the pneumonic areas contained cellular debris. There were variable numbers of erythrocytes and polymorphonuclear and mononuclear leucocytes in some of the alveoli adjoining the largest areas of consolidation. The pulmonary lymphoid tissue was hypertrophic.

Both the chest roentgenograms and the roentgenograms of the excised lungs of the rabbits killed on the 1st day contained abnormal homogeneous shadows. The shadows in the latter proved to depict the location and extent of the lesions better than the chest roentgenograms. The abnormal shadows were cast by areas of tuberculous pneumonia in a state of red hepatization.

There was no significant change in the shadows of roentgenograms taken on the 1st and the 2nd days, yet the shadows in roentgenograms taken on the 2nd day were cast by areas of tuberculous pneumonia in a state of gray hepatization. The following is the protocol of a rabbit killed on the 2nd day:

Rabbit No. 74: Killed on the 2nd day: There were homogeneous shadows in the chest roentgenograms taken on the 1st and the 2nd days. The roentgenograms of the excised lungs contained a large homogeneous shadow with indefinite margins, comparable to the shadow in the roentgenograms of the excised lungs of the rabbit killed on the 1st day. Necropsy examination disclosed large areas of predominantly gray consolidation in the medial and dorsal portions of both the left upper and the left lower lobes. The left lung did not inflate as well as the right lung. The paratracheal lymph nodes were large and soft. There was a fluctuating cold abscess in the subcutaneous tissues of the groin. There were no gross tuberculous lesions in any other parts of the body. The sections disclosed several large and a few small pneumonic areas. The pneumonic areas were in many respects similar to those in the lungs of the rabbits killed on the 1st day. There were, however, more mononuclear leucocytes in the alveoli. The septa were thicker and contained more leucocytes and erythrocytes. Fewer dilated capillaries were found. One of the paratracheal lymph nodes showed hypertrophy and hyperplasia of the reticular elements. The sinuses of this node contained a few mononuclear leucocytes. (Some of the roentgenological and pathological findings of rabbits 73 and 74 are illustrated in plate I.)

As a rule the shadows in chest roentgenograms taken on the 4th day were similar to the shadows in roentgenograms taken on earlier days.

The lungs of rabbits killed on the 4th day, however, showed isolated foci of anaemic necrosis in the consolidated areas. The roentgenological and pathological findings of a rabbit killed on the 4th day are as follows:

Rabbit No. 75: Killed on the 4th day: There were comparable shadows in the chest films taken on the 1st, 2nd, and 4th days. The shadows were homogeneous and had indefinite margins. The film of the excised lungs contained a large homogeneous shadow, situated in the left lung field, and two elliptical shadows, located near the outline of the trachea. The margins of the large homogeneous shadow were in part clearly defined and in part vaguely defined. Postmortem examination of the lungs disclosed extensive areas of gray consolidation in the medial and dorsal portions of the left upper and lower lobes. These areas did not inflate as well as the other parts of the lungs. The paratracheal lymph nodes were slightly enlarged. Apart from the above described lesions and fluctuating cold abscesses in the groins, no gross tuberculous lesions were found in other parts of the body. The sections showed extensive pneumonic areas containing isolated foci in which the blood-vessels were thrombosed and the tissues were undergoing necrosis. There were large numbers of polymorphonuclear leucocytes in the vicinity of the necrotic foci. The lesions were in other respects similar to those of the rabbits killed on the 2nd day.

There was usually no significant change in the size or the character of the abnormal shadows in roentgenograms taken between the 4th and 8th days, yet the lungs of every rabbit killed on the 8th day contained areas of gray consolidation with one or more macroscopic caseous foci. The following protocol gives the findings in a rabbit killed on the 8th day:

Rabbit No. 77: Killed on the 8th day: There were homogeneous shadows in the left lower lung field of all of the chest roentgenograms taken between the 1st and the 8th days. The shadows had vaguely defined margins. The shadows in the films taken on the 1st and the 8th days were similar. The roentgenogram of the excised lungs contained a homogeneous shadow, situated in the left lung field, and some oval shadows superimposed upon the outline of the trachea. The margins of the large homogeneous shadow were in part clearly defined and in part vaguely defined. Necropsy examination of the lungs showed a pyramidal area of red gelatinous-appearing consolidation in the left lower lobe. This area contained one yellow focus measuring 2 mm. in diameter. The paratracheal lymph nodes were large, soft and gray. No evidence of tuberculosis in the groin, or elsewhere in the body, was found. The sections showed a large pneumonic area and isolated pneumonic areas in the left lower lobe. The latter were in the lower half of the lobe. Both the large and the small consolidated areas contained macroscopic necrotic or caseous foci. The

necrotic foci consisted of amorphous debris infiltrated with polymorphonuclear leucocytes in part and undergoing caseation in part. The blood-vessels appeared to be obliterated and the few bronchi identified were undergoing ulceration. There were many large mononuclear and polymorphonuclear leucocytes, some clusters of lymphocytes, some erythrocytes and a few fibroblasts at the margins of the necrotic and caseous foci. No giant cells were found. In some places the alveoli adjoining the areas of consolidation contained large numbers of monouclear leucocytes; in other places, they contained practically no cells. In the areas in which there were many leucocytes in the alveoli, the septa were thick. (Some of the roentgenological and pathological findings of rabbit 77 are illustrated in plate II.)

In many instances the shadows in chest roentgenograms taken during the 2nd week were larger than those in roentgenograms taken during the 1st week. In spite of this fact the shadows usually retained the original characteristics. The lungs of all the rabbits killed during the 2nd week contained extensive areas of gray consolidation with one or more macroscopic and many microscopic caseous foci. This point is sufficiently important to warrant another example:

Rabbit No. 271: Killed on the 12th day: There were homogeneous shadows in the left lower lung fields of the chest roentgenograms taken on the 1st and the 12th days. These shadows had clearly defined margins and were of comparable density. The roentgenogram of the excised lungs contained a large homogeneous shadow with indefinite margins, scattered mottled shadows and some triangular shadows. The large homogeneous and mottled shadows were situated in the left lower lung field, the triangular shadows, near the outline of the trachea. Postmortem examination of the lungs disclosed an area of red to gray consolidation in the apex of the left lower lobe and many minute areas of gray consolidation scattered through this lobe. When the lungs were inflated in the negative-pressure chamber the large consolidated area appeared recessed in healthy lung and many of the small lesions were no longer visible. Two paratracheal lymph nodes, on the left side of the trachea, were large, soft and brown. There was a cold abscess in the left groin of the animal. These were the only tuberculous lesions found in the animal. The sections showed an extensive pneumonic area in the left lower lobe and isolated pneumonic foci scattered throughout the left lung. The consolidated parts contained many areas of anaemic necrosis and caseation. Surrounding the necrotic and caseous areas there were variable numbers of polymorphonuclear leucocytes, a few giant cells and in places some fibroblasts. In parts of the consolidated areas the septa were not identified; in other parts they were very thick. Some of the small bronchi in these areas were compressed and distorted. The lumina

of such bronchi contained cellular exudate and debris. The alveoli adjoining the large pneumonic areas contained variable numbers of mononuclear leucocytes. In contrast to this some of the isolated pneumonic foci were surrounded by lymphocytes and sharply separated from the adjoining parenchyma. The pulmonary lymphoid tissue was hypertrophic. A paratracheal lymph node, the sinuses of which were dilated and contained many mononuclear leucocytes and some exudate, showed hypertrophy and hyperplasia of both the lymphoid and the reticular elements.

Complications

Evidence of miliary dissemination and of cavity-formation was detected in some of the chest roentgenograms taken during the 2nd week. One rabbit killed in this period had, in addition to tuberculous pneumonia, an acute pleurisy with effusion. Two had a tuberculous pneumonia complicated by miliary tuberculosis. Several had a caseous pneumonia with one or more cavities. The following protocol gives the roentgenological and pathological findings of the rabbit that had acute pleurisy with effusion:

Rabbit No. 273: Killed on the 8th day: The chest roentgenograms taken on the 1st day contained a large abnormal shadow situated in the left lung field. A posteroanterior film made on the 8th day showed a homogeneous shadow occupying the upper two-thirds of the left lung field. No abnormal shadows were detected in the right lung field of any of the roentgenograms taken during life. The roentgenograms of the excised lungs revealed a large dense shadow with indefinite margins in the left lung field, minute indistinct shadows in the right lung field and elliptical shadows on both sides of the outline of the trachea. At necropsy the pleurae on the left side were acutely inflamed. Short stout adhesions bound the left lower lobe to the lateral chest-wall and formed a pocket in which there were approximately 7 cc. of grumous pus. The apical portion of the left lower lobe was adherent to the dorsal chest-wall. Most of this lobe and all of the left upper lobe were solid. On cut surface it was plain that the consolidated areas contained several caseous foci. The right lung was irregularly studded with minute gray tubercles. The paratracheal lymph nodes were very large. There was a cold abscess in the subcutaneous tissues of the groin and the common iliac lymph nodes were unusually prominent. No gross tuberculous lesions were found elsewhere in the body. The sections confirmed the macroscopic necropsy findings. They also revealed many minute necrotic and caseous foci in the consolidated parts of the left lung and a few such in the tubercles of the right lung. The cellular characteristics of the lesions were similar to those of other rabbits killed on the 8th day. (A chest roentgenogram and a photograph of a large section of the lungs of rabbit 273 are shown in plate III.)

Although the shadows in the final chest roentgenograms of the foregoing case were unusually large, neither the location nor the character of the shadows suggested a pneumonic process complicated by a pleural effusion. The chest roentgenograms failed to reveal any evidence of disease in the right lung, yet the roentgenograms of the excised lungs showed many minute shadows in the right lung field. At necropsy a tuberculous pneumonia, complicated by an acute pleurisy with effusion, was found on the left side and miliary tubercles were found in the right lung.

The roentgenological and pathological findings of a rabbit in which miliary tuberculosis developed are as follows:

Rabbit No. 124: Killed on the 15th day: No abnormal shadows were detected in any of the chest roentgenograms taken before the 10th day. A film made on the 10th day revealed minute shadows throughout both lung fields. Similar shadows were found in the films made on the 12th and 15th days. In addition, a faint homogeneous shadow was first detected in the film taken on the 15th day. The roentgenogram of the excised lungs showed miliary shadows in both lung fields, some coarsely mottled shadows in the left lower lung field and two triangular shadows near the outline of the trachea. The postmortem findings were as follows: The left pleural cavity contained approximately 5 cc. of clear serous fluid. The left lung, except for the left lower lobe which contained several scattered and confluent areas of gray consolidation, and all of the right lung were studded with minute miliary tubercles. The paratracheal lymph nodes were very large. There was an encapsulated caseous abscess in the subcutaneous tissues of the groin. The spleen was large, but contained no macroscopic tubercles. No gross tuberculous lesions were found in the liver, kidneys, brain and meninges. The sections showed lobular pneumonic areas in the left lower lobe and miliary tubercles scattered throughout both lungs. The pneumonic areas contained irregularly shaped caseous foci partially surrounded by polymorphonuclear leucocytes, lymphocytes and fibroblasts. Only a few giant cells were found. The bronchi in the consolidated parts were compressed. Only the large blood-vessels appeared to be patent. Many of the alveoli adjacent to the consolidated areas contained mononuclear leucocytes. The miliary tubercles were of varied size and shape. They consisted of clumps of mononuclear leucocytes surrounded by lymphocytes and fibroblasts. A few contained caseous foci and an occasional giant cell. There were inflammatory changes in the pleura over one tubercle. The pulmonary lymphoid tissue was hypertrophic and hyperplastic. The paratracheal lymph nodes showed changes similar to those of the rabbits killed on the 12th day. (A roentgenogram of the excised lungs and a photograph of a large section of the lungs of rabbit 124 are shown in plate III.)

In the case just described a diagnosis of miliary tuberculosis was made from the shadows in a chest film taken on the 10th day. The diagnosis was confirmed by the necropsy findings.

The following is the protocol of a rabbit which was killed at the end of the 2nd week and which had an extensive caseous pneumonia with several cavities:

Rabbit No. 123: Killed on the 14th day: There were homogeneous shadows in the lower half of the left lung field of all of the chest roentgenograms taken after the intratracheal injection of tubercle bacilli. The abnormal shadows in the chest films made on the 14th day were slightly larger than those in the films made earlier and contained one rarefied area suggestive of a cavity. The roentgenograms of the excised lungs showed a dense shadow containing four rarefied areas in the left lung field and some oval shadows overlying the outline of the trachea and main-stem bronchi. Inspection of the lungs disclosed sharply demarcated areas of red to gray consolidation in the left upper lobe and in portions of the left lower lobe. There were a few minute yellow foci in the consolidated areas. One of the paratracheal lymph nodes was unusually large. There was an encapsulated cold abscess in the groin. The viscera, apart from the left lung, contained no gross tuberculous lesions. Large sections showed areas of tuberculous pneumonia in the left lung corresponding in size and location to the shadows in the roentgenograms of the excised lungs. These areas contained many necrotic and caseous foci. Some of the caseous foci were situated in the periphery of the lung. Where this was the case the adjacent pleura was invariably thick. The large bronchi in the consolidated areas were patent. However, they showed signs of ulceration and contained variable amounts of necrotic debris. Small sections were prepared to permit of histological examination of the cavities which were not included in the large sections. These showed an area of tuberculous pneumonia containing several areas of necrosis and caseation and one cavity. The cavity was situated close to the visceral pleura. The inner surface of the cavity consisted of necrotic debris in which a few polymorphonuclear leucocytes were identified. The wall of the cavity was composed of mononuclear leucocytes, lymphocytes and fibroblasts. There were minute blood-vessels in the areas in which the fibroblasts were abundant. One medium-sized bronchus communicated with the cavity. This bronchus contained some cellular debris. No evidence of ulceration of the bronchial wall was found. Small sections stained by Weigert's method showed that there was elastic tissue in alveolar arrangment in the consolidated areas adjoining the cavity described above. The elastic tissue extended up to the inner necrotic part of the cavity. Some of the debris inside the cavity contained stainable elastic tissue in alveolar arrangement. (A roentgenogram of the excised lungs and photographs of a large section and a small section of the lungs of rabbit 123 are shown in plate III.)

The final chest roentgenogram of the rabbit described in the above protocol contained shadows indicative of consolidation and possibly cavity. The roentgenogram of the excised lungs, however, clearly revealed an extensive area of consolidation containing four cavities. Examination of the lungs showed areas of tuberculous pneumonia in both the left upper and the left lower lobes. These contained 4 recently formed cavities and multiple poorly demarcated caseous foci. Sections of the lesions corroborated the gross findings and showed among other things elastic tissue in alveolar arrangement in the necrotic material of one of the cavities and ulcers in some of the larger bronchi.

For the sake of convenience, the presentation of the roentgenological and pathological findings of the rabbits killed after the 2nd week will be divided into two parts, the first dealing with the findings in animals with pulmonary cavities and the second dealing with the findings in animals without pulmonary cavities.

Rabbits with Cavities

Signs of cavity were detected in several chest roentgenograms taken between the 2nd and 4th weeks. The lungs of two of the 4 rabbits killed in the latter half of the 1st month contained cavities. This evidence indicates that under the present experimental conditions cavity-formation was a common occurrence in the early stages of reinfection pulmonary tuberculosis.

The following protocol gives the roentgenological and pathological findings of a rabbit in which cavity-formation probably occurred during the 1st month and in which a partially healed cavity was found when the animal was killed in the 4th month:

Rabbit No. 45: Killed at 14¾ weeks: The chest roentgenograms taken during the 2nd and the 4th weeks contained abnormal homogeneous shadows with indefinite margins. These shadows occupied the lower two-thirds of the left lung field. The abnormal shadows in films taken in the latter part of the 2nd month were smaller but still had indefinite margins. The shadows in the roentgenograms made during the 3rd and 4th months were different from the shadows of earlier roentgenograms in that they were denser and had more clearly defined margins. Evidence of cavity was not detected in any of the chest roentgenograms. The roentgenograms of the excised lungs, however, disclosed coarse mottled shadows, stippled with minute unusually dense shadows, and shadows indicative of cavity. They also showed oval shadows near the outline of the trachea. The following notes on the appearance of the excised lungs were made before the lungs were cut: The left lung was slightly

larger than the right lung. There were numerous areas of gray consolidation containing yellow foci of varied size, in the left lower lobe. There were a few minute gray tubercles with yellow cores in the dorsal portion of the right lower lobe. The paratracheal lymph nodes on both sides of the trachea were large, soft and brown. There was a cold abscess in the groin. Sections of the left lower lobe disclosed 50 or more macroscopic caseous foci and an irregularly shaped cavity medial to the main bronchus. Some of the caseous foci contained purplish plaques suggestive of calcareous deposits. Lymphocytes and fibroblasts, interspersed with giant cells, surrounded many of the caseous foci and separated them from the surrounding parenchyma. In places the intervening alveoli contained variable numbers of mononuclear leucocytes. At one point two caseous foci had apparently invaded the wall of the main bronchus and caused constriction of the lumen of the bronchus. The bronchial mucosa at the site of constriction was necrotic. The walls of the cavity consisted of necrotic and caseous material, leucocytes and immature fibrous tissue in varied proportions. Mononuclear and polymorphonuclear leucocytes were usually found in the vicinity of caseous material. Lymphocytes were abundant where there were fibroblasts and fibrous tissue. The pleura adjacent to the cavity was very thick. The sinuses of the paratracheal lymph nodes were packed with pale mononuclear cells. (Some of the roentgenological and pathological findings of rabbit 45 are illustrated in plate IV.)

Evidence of cavity, or of minute calcareous deposits, was not detected in any of the chest roentgenograms of the foregoing case. Roentgenograms of the excised lungs, however, contained shadows indicative of a cavity and of minute calcareous deposits in areas of consolidation. The sections showed a cavity in the medial and diaphragmatic part of the left lower lobe. The walls of the cavity consisted of necrotic and caseous material, fibroblasts, lymphocytes and variable numbers of large mononuclear and polymorphonuclear leucocytes. The sections also showed many fibrocaseous tubercles, some of which contained calcareous material.

The roentgenological and pathological findings of a rabbit in which a pulmonary cavity was found when the animal was killed in the 6th month are described in the following protocol:

Rabbit No. 47: Killed at 21¼ weeks: The abnormal shadows in the chest roentgenograms taken in the 1st month were comparable to those in the roentgenograms of the rabbit killed in the 4th month. The shadows in roentgenograms made in the 2nd month were similar but smaller. No abnormal shadows were found in roentgenograms taken during the last month of life of the animal. There were, however, in the left lung field of the roentgenogram of the

excised lungs some faint irregularly-shaped homogeneous shadows and an oval shadow indicative of a thin-walled cavity. The roentgenogram of the excised lungs, as in other instances, contained elliptical shadows adjacent to the outline of the trachea. Postmortem examination of the lungs disclosed an irregularly-shaped area of gray consolidation which extended from a yellow nodule in the apex of the left lower lobe to the lateral and the diaphragmatic portions of this lobe. There were in addition to the lesion just mentioned, a few small gray tubercles in both the left lower and the right lower lobes. A paratracheal lymph node on the left side of the trachea was unusually large, measuring 1 x 0.5 x 0.3 cm. in the various diameters. The sections showed many fibrocaseous and fibrous lesions of varied size and shape in the vicinity of the main bronchus of the left lower lobe and a cavity in the apex of this lobe. Some of the caseous lesions were small and discrete; others had many ramifications. The discrete lesions were well surrounded by lymphocytes, fibroblasts and fibrous tissue. The ramifying lesions were surrounded in part by dense bands of fibrous tissue which contained many lymphocytes, and in part by collections of mononuclear and polymorphonuclear leucocytes and a few fibroblasts. Some of the alveoli adjoining these lesions contained large numbers of mononuclear leucocytes; others were distinctly emphysematous. Many of the interalveolar septa were thick and tortuous. Some of the small bronchi and blood-vessels in proximity to the fibrocaseous lesions appeared compressed and distorted. The cavity presented a histological picture similar to that of the cavity in the lung of the rabbit killed in the 4th month. The inner part of the wall of the cavity consisted of necrotic and caseous material. The outer part contained mature fibrous tissue infiltrated with lymphocytes. There was a caseous focus near the cavity. This contained a few purplish plaques suggestive of calcareous material. Some of the adjacent alveoli were markedly emphysematous. The tubercles in the right lung had high proportions of lymphocytes. There was an increase in the reticular elements of a large paratracheal lymph node. A section stained for elastic tissue failed to show elastic tissue in the larger caseous foci though present in other parts of the lungs. There was a break in the continuity of the elastic tissue of the main bronchus of the left lower lobe. (Some of the roentgenological and pathological findings of rabbit 47 are illustrated in plate V.)

From the foregoing protocol and the reproductions of the roentgenograms it is plain that although no evidence of disease was found in a chest roentgenogram made the day the rabbit was killed, a roentgenogram of the excised lungs, taken the same day, revealed evidence of disease. There were faint homogeneous shadows with indefinite margins and an annular shadow in the left lung field of the roentgenogram of the excised lungs. A comparison of the shadows and the pulmonary lesions

showed that the faint homogeneous shadows were cast by fibrocaseous and fibrous lesions and that the annular shadow was cast by a cavity with a predominantly necrotic and caseous wall.

The lungs of a few rabbits killed between the 6th month and the 2nd year contained cavities in various stages of healing. The roentgenological and pathological findings of a rabbit killed 2 years after the intratracheal injection are as follows:

Rabbit No. 82: Killed at 102⅞ weeks: A chest roentgenogram taken at 2¼ weeks revealed very large and dense shadows in the lower half of the left lung field. A film taken in the latter part of the 2nd month contained smaller and less dense shadows. No abnormal shadows were found in any of the chest films made after the 5th month. Evidence of disease, however, was found in the roentgenogram of the excised lungs. This evidence consisted of an unusually large and indistinct left upper lung field and a small left lower lung field which contained a few homogeneous shadows with indefinite margins and a faint circular shadow. The lungs presented the following features before they were cut for sections: The right lung appeared natural in all respects. The left upper lobe was emphysematous. There were a few adhesions in the interlobar fissure. The left lower lobe was about one-half normal size. The apex of the lobe contained an area of gray consolidation and some scar-tissue. Distal to the apex there were a few gray tubercles. In the distal and diaphragmatic portions of the lobe there were several gray tubercles one of which contained a macroscopic caseous area. The paratracheal lymph nodes were not appreciably enlarged. No changes of significance were found in the sections of the right lung. The sections of the left lung disclosed many points of interest. The left upper lobe was markedly emphysematous. The left lower lobe was small and irregular in outline. The pleura covering it contained much hyaline fibrous tissue and some lymphocytes. There was a cluster of dilated bronchi, surrounded by fibrous tissue and areas of compensatory emphysema, in the central part of the lobe. Adjacent to one of the dilated bronchi there were two elliptical cavities measuring 3 mm. in the longest diameters. The inner aspects of the walls of both of these cavities were necrotic. In the lateral and diaphragmatic portions of the lobe there were, in addition to an occasional minute fibrocaseous lesion, some tubercles consisting of large mononuclear leucocytes and lymphocytes. (Plate VI contains illustrations of some of the roentgenological and pathological findings of the rabbit described in the above protocol.)

All of the chest roentgenograms of the foregoing case, taken before the 5th month, contained abnormal shadows. No abnormal shadows, however, were found in any of the chest roentgenograms taken after the

5th month, although roentgenograms were made at monthly intervals for a period of one and one-half years. In contrast, when the animal was killed at the end of two years, roentgenograms of the excised lungs disclosed evidence of disease. This evidence consisted of an unusually large and indistinct left upper lung field and a small left lower lung field, which contained a few homogeneous shadows with indefinite margins and a faint circular shadow. Sections of the lung showed that the left upper lobe was markedly emphysematous and that the left lower lobe was small and irregular in outline and contained a number of dilated bronchi surrounded by fibrous tissue and areas of emphysema, two minute cavities and a few tubercles. A comparison of the roentgenological and pathological findings brought out the following points: No evidence of the lesions discovered at necropsy was found in the chest roentgenograms. Some of the small homogeneous shadows with indefinite margins in the left lung field of the roentgenogram of the excised lung were cast by fibrous tissue surrounding abnormal bronchi, while others were cast by clusters of recent tubercles and minute fibrocaseous lesions. The circular shadow in the roentgenogram of the excised lung, was cast by the dilated bronchi and not by a cavity. No evidence of the two small cavities was found in even the roentgenograms of the excised lungs.

Although the findings of most of the rabbits with pulmonary cavities, killed after the 6th month, were similar to those given in the preceding protocol, the findings of one animal were different. In the case of this animal there was a striking change in the course of the disease during the 10th month, as the following protocol indicates:

Rabbit No. 83: Killed at 127¾ weeks: The abnormal shadows in the early chest roentgenograms were comparable to those in the roentgenograms of the other rabbits of this series. Evidence of recession of the shadows, however, was detected at a later date. A film made at 38¾ weeks revealed a small homogeneous shadow with a few unusually dense areas situated in the midportion of the left lung field. A film made a fortnight later, namely, at 40 weeks, showed a striking change. No shadows were found in the central portion of the left lung field, but a large shadow was found in the lowermost portion of the left lung field. In films taken subsequently an area of rarefaction was detected in the shadow at the base of the left lung field. In films made during the 2nd and 3rd years the shadows were very dense and signs of cavity were detected at times and not detected at other times. No evidence of cavity was found in the final chest roentgenogram. The roentgenogram of the excised lungs con-

tained many dense discrete shadows and a circular shadow, all of which were situated in the base of the left lung field. At necropsy the right lung appeared natural in all respects. The left upper lobe was moderately emphysematous. The left lower lobe was small and irregular in outline. Even before the lobe was cut for sections it was plain that there were many caseous lesions and a few calcareous deposits in the lowermost portion of the lobe. The paratracheal lymph nodes were slightly larger than usual. They contained no macroscopic caseous or calcareous material. The sections showed a small left lower lobe surrounded by pleura which was thick, and chronically inflamed in places. The sections examined contained portions of several cavities, many caseous and calcareous foci, much fibrous tissue, some small areas of emphysema and some abnormal bronchi. The bronchi were unusually large and tortuous. One, which was adjacent to a large caseous focus, was partially ulcerated.

The roentgenological picture of the rabbit described in the foregoing protocol was unusual in the following respects: *1:* The shadows in the roentgenograms taken between the 2nd and the 10th months receded slowly. *2:* A film made in the early part of the 10th month revealed a faint shadow containing a few minute dense shadows in the midportion of the left lung field. *3:* A film made two weeks later failed to reveal any shadows in this site, but disclosed a large shadow in the basal portion of the left lung field. *4:* Films taken in the following one and one-half years revealed evidence of cavitation and calcification in the new area of disease. Postmortem examination of the lungs showed an emphysematous left upper lobe and a small left lower lobe containing several cavaties, many caseous and calcareous foci, much fibrous tissue, some small areas of compensatory emphysema and some abnormal bronchi.

Rabbits without Cavities

In a preceding section the roentgenological and pathological findings of rabbits, killed before complications began to occur, were described. In the present section the roentgenological and pathological findings of rabbits which were killed after the 2nd week and which did not show such complications as pleural effusion, miliary dissemination and cavitation, will be given. Since the shadows in the serial roentgenograms of most of the rabbits were comparable and since areas of caseous pneumonia were found in every animal killed during the 2nd week, it is reasonable to assume that all of the rabbits had at an early stage tuberculous lesions containing caseous foci. As a rule the shadows in chest roentgenograms made in the 3rd week differed little from those in roent-

genograms taken in the 2nd week, yet the lesions despite the presence of caseous foci were beginning to heal. The following protocol, of a rabbit killed during the 3rd week, illustrates this point:

Rabbit No. 125: Killed at 3 weeks: All of the chest roentgenograms taken between the 1st day and the 3rd week showed abnormal shadows in the lower half of the left lung field. The shadows in the first and the last films were comparable. The roentgenograms of the excised lungs showed extensive homogeneous shadows with indefinite margins and mottled shadows in the left lung field. They also revealed oval shadows adjacent to the outline of the trachea. The lungs presented the following features: In the collapsed state the left lung appeared twice as large as the right lung. The upper lobe of the left lung contained one large gray pneumonic area and scattered pneumonic foci of varied size and shape. The lower lobe of the left lung contained several large gray pneumonic areas. These areas, as viewed through the visceral pleura, appeared sharply separated from the surrounding pulmonary tissue. The paratracheal lymph nodes were large, soft and gray. The sections showed lesions in the left lung which corresponded roughly in location and extent to the shadows in the roentgenograms of the excised lungs. There were isolated and clustered tubercles and one moderately large pneumonic area in the left upper lobe. The latter contained areas of necrosis and caseation as well as areas in which organization had begun. There were scattered tubercles and large pneumonic areas, similar to that described above, in the left lower lobe. Some of the bronchi of this lobe contained caseous debris. A portion of the mucosa of one large bronchus was infiltrated with polymorphonuclear leucocytes. The pleura adjoining the pneumonic areas showed signs of a chronic inflammatory process. The paratracheal lymph nodes exhibited hypertrophy and hyperplasia of the lymphoid and reticular elements. (Plate VII contains reproductions of the essential roentgenological and pathological findings of the rabbit described above.)

As a rule, no essential difference was detected in the shadows of chest roentgenograms, or of roentgenograms of the excised lungs, taken in the 2nd and 3rd weeks. In contrast to this, the lesions of rabbits killed in the 2nd and the 3rd weeks invariably showed significant differences. The caseous foci in the pneumonic areas of the former were poorly separated from the surrounding tissues, whereas the caseous foci in the pneumonic areas of the latter were well surrounded by fibroblasts and fibrous tissue infiltrated with lymphocytes. Signs of organization of the pneumonic exudate were usually absent in the former, though present in the latter as described in the foregoing protocol.

Frequently, as indicated by the data in table 2, the abnormal shadows in chest roentgenograms taken during the 2nd month were smaller than those in roentgenograms taken in the latter part of the 1st month. The

TABLE 2

CASE NUMBERS	NUMBER OF RABBITS	APPROXIMATE DATE OF LARGEST ABNORMAL SHADOWS	APPROXIMATE DATE OF BEGINNING CLEARING OF SHADOWS	APPROXIMATE DATE OF DISAPPEARANCE OF SHADOWS	DURATION OF EXPERIMENT
			months	*months*	
121–129 B	5				
125		3 weeks	—	—	3 weeks
122		2 weeks	—	—	3 weeks
127		2 weeks	1	—	1¼ months
128		2 weeks	1	—	1¼ months
129		2 weeks	1	2	2½ months
39–48 B	4				
45		2 weeks	2	—	3½ months
46		1 month	1½	3½	3½ months
47		2 weeks	1¾	5½	5½ months
48		1¼ months	2	4½	5½ months
205–213	9				
208		1 week	1½	2	4 months
210		2 weeks	1½	2	7 months
213		2 weeks	2	6	8 months
211		1 week	1½	4	10½ months
212		1 week	1½	4	10½ months
205		1 week	1½	4	1 yr., 5 months
207		1 week	1½	4	1 yr., 5 months
206		1 week	1½	4	1 yr., 5 months
209		2 weeks	1½	5	1 yr., 5 months
134–138	5				
136		2 weeks	1¾	5	9 months
137		2 weeks	1	5	9 months
138		2 weeks	1	5	1 year
135		2 weeks	1¾	4	1 yr., 10 months
134		3 weeks	1	4	2 years
80–88 B	3				
84		4 weeks	2	5	1 year
82		2 weeks	2	5	2 years
83		3 weeks	2¼	—	2 yrs., 6 months

pulmonary lesions of rabbits killed in the 2nd month showed signs of healing both by organization and by resolution. The following protocol is typical of the protocols of rabbits killed in the 2nd month:

Rabbit No. 127: Killed at 5 weeks: Homogeneous shadows with indefinite margins were present in the lower half of the left lung field of all the chest roentgenograms. A chest film taken at the end of the 2nd week contained the largest and densest shadows. The shadows in the last chest film were comparable to those in the chest films taken on the 1st day. The roentgenogram of the excised lungs revealed poorly defined shadows of varied size and shape scattered through the lower half of the left lung field and ovoid shadows superimposed upon the outline of the trachea. As the lungs lay in the open chest the left lung appeared twice as large as the right lung. Several confluent gray pneumonic areas containing minute yellow foci were found in the dorsal and the diaphragmatic portions of the left lower lobe. These areas appeared to be sharply separated from the adjacent pulmonary tissue. The paratracheal lymph nodes were very large. The sections showed a large pneumonic area, containing necrotic and caseous foci, in the apical portion of the left lower lobe and several similar though smaller pneumonic areas in other portions of the lobe. The necrotic and caseous foci in the large area of consolidation were surrounded by polymorphonuclear and mononuclear leucocytes and fibroblasts. The main bronchi in this area were patent but contained cellular debris. Some of the blood-vessels were thrombosed. The caseous foci in the smaller pneumonic areas were of microscopic proportions. They contained a few polymorphonuclear leucocytes and an occasional giant cell. They were well surrounded with fibroblasts, fibrous tissue and lymphocytes. In places the interalveolar septa were unusually thick and the alveoli were filled with large mononuclear leucocytes. In other places, although the septa were thick, the the alveoli contained no leucocytes and no exudate.

The shadows in the chest roentgenogram of the foregoing case, taken on the 1st day, were similar to the shadows in the chest roentgenogram taken at the end of the 5th week. It is plain, however, from a comparison of the pathological findings of other rabbits killed at earlier dates and the pathological findings of this case, that the lesions which cast the shadows in the first film and the last film were different. The former lesions were progressive; the latter, retrogressive.

Many of the chest roentgenograms taken during the 3rd and 4th months failed to disclose evidence of disease, as the data in table 2 indicate. The roentgenograms of the excised lungs of rabbits killed during these months, however, usually revealed signs of disease. The following protocol describes the roentgenological and pathological findings of a rabbit killed during the 4th month:

Rabbit No. 46: Killed at 14¾ weeks: The shadows in the early chest roentgenograms were comparable to those in the early chest roentgenograms of the rabbit

described in the preceding protocol. A roentgenogram taken in the 4th week revealed large shadows in the lower half of the left lung field. The shadows in a film taken in the 6th week were similar but smaller. No abnormal shadows were detected in a posteroanterior film, made the day the animal was killed. The roentgenogram of the excised lungs, however, showed some mottled shadows in the right lung field, a few similar shadows and a homogeneous shadow with irregular and indefinite margins in the left lung field, and two oval shadows adjacent to the outline of the trachea. The lungs, as they lay in the open chest, appeared of equal size. The right lower lobe contained a cluster of gray tubercles, two of which at least had caseous cores. The left lower lobe contained a similar though larger cluster of tubercles. The paratracheal lymph nodes were large, soft and brown. The microscopic findings corroborated the macroscopic findings. The tubercles in the right lower lobe were small. They were well surrounded by fibroblasts, fibrous tissue and lymphocytes. Only a few contained caseous foci. Many of the tubercles in the left lower lobe were larger than those in the right lower lobe. These as well as the smaller tubercles were surrounded by fibroblasts, fibrous tissue and lymphocytes. Some of the tubercles had caseous cores. A few giant cells were found among the fibroblasts and lymphocytes at the periphery of the caseous material. The interalveolar septa adjacent to the larger tubercles were abnormally thick and tortuous. Some of the alveoli in the vicinity of a cluster of subpleural tubercles were emphysematous. Sections stained by Weigert's method showed elastic tissue in many of the thick and tortuous septa but failed to reveal elastic tissue in the fibrocaseous tubercles.

In the foregoing case, as in others, a chest roentgenogram taken in the 4th month was the first in which no abnormal shadows were found. A roentgenogram of the excised lungs, however, revealed mottled shadows in the lower portions of both lung fields. These shadows were cast by clusters of fibrous and fibrocaseous tubercles.

Although no abnormal shadows were found in many of the chest roentgenograms made after the 6th month, the roentgenograms of the excised lungs of the majority of the animals presented evidence of residual lesions. The lesions found at necropsy proved to be varied. For example, one of two rabbits injected with the same suspension of bacilli and killed about the same time showed healing by fibrosis; the other, healing by calcification. The protocols of these two animals are as follows:

Rabbits Nos. 136 & 137: Killed at 33¼ and 34½ weeks respectively: The early chest roentgenograms of both animals contained homogeneous shadows limited to the left lower lung fields. The shadows were largest in films taken in

the 2nd week. They showed signs of recession in a film taken late in the 2nd month in the case of the first rabbit, and in a film taken at the end of the 1st month in the case of the second rabbit. No abnormal shadows were recognized in any chest films (posteroanterior) taken after the 5th month. Roentgenograms of the excised lungs of both rabbits, however, revealed evidence of disease. The roentgenogram of the first rabbit showed a small left lung field containing some short slender shadows. A lipiodol study pointed to a constriction of the main bronchus of the left lower lobe. The roentgenogram of the second rabbit showed a slightly reduced left lung field containing two minute unusually dense shadows. Postmortem examination showed that the left lower lobe of each rabbit was smaller than usual. The left lower lobe of the first rabbit contained a number of grooves in one of which there was an area of gray consolidation. A constriction in the main bronchus was found when the lobe was cut. The left lower lobe of the second rabbit contained a V-shaped area of gray consolidation in the apex of which two small calcareous tubercles were found when the lobe was cut. The sections of the lungs of the first rabbit showed a left lower lobe of reduced size and irregular outline. Strands of solid tissue, composed of interalveolar septa and fibrous tissue infiltrated with lymphocytes, stretched from two of the largest indentations in the lobe to the area of constriction in the main bronchus. Some of the alveoli adjacent to these strands of solid tissue were emphysematous. No evidence of ulceration of the main bronchus was found. The picture presented by the sections of the lungs of the second rabbit was quite different. There was but one area of puckering in the left lower lobe. From this, short strands of hyaline fibrous tissue enclosing two calcareous and several caseous foci extended approximately 1 cm. into the pulmonary parenchyma. In the periphery of the caseous foci there were large mononuclear leucocytes and a few giant cells. Some of the alveoli adjacent to these lesions contained clumps of mononuclear leucocytes; others were markedly emphysematous. No lesions were found in other parts of the lungs. (Some of the roentgenological and pathological findings of rabbits 136 and 137 are illustrated in plate VIII.)

The shadows in the serial chest roentgenograms of the two rabbits described in the above protocols were comparable. The rabbits were killed at the end of the 8th month. Roentgenograms of the excised lungs disclosed evidence of pulmonary disease. The roentgenogram of the first case showed a small left lung field containing a few short linear shadows. A lipiodol study revealed evidence of a constriction in the main bronchus of the left lower lobe. The roentgenogram of the second case disclosed two small unusually dense shadows in the lowermost part of the left lung field. (In retrospect it seems probable that abnormal

shadows would have been found in this area if a lateral chest roentgenogram had been made during the latter part of the life of the animal.) The left lower lobe of the first rabbit showed on postmortem examination strands of fibrous tissue infiltrated with lymphocytes, an area of constriction in the main bronchus and some emphysematous alveoli. The left lower lobe of the second rabbit contained but one small area of disease. This area was composed of a cluster of minute caseous and calcareous tubercles surrounded by hyaline fibrous tissue, and a few alveoli containing clumps of large mononuclear leucocytes. Some of the alveoli adjoining this area were emphysematous.

In a few instances in which no abnormal shadows were detected in chest roentgenograms taken after the 6th month, no evidence of disease was found in the roentgenograms of the excised lungs. In some of these cases no lesions were found at necropsy. The following protocol describes the roentgenological and pathological findings of one such case:

Rabbit No. 84: Killed at 59¾ weeks: A chest roentgenogram made on the 1st day disclosed faint homogeneous shadows in the left lower lung field. The abnormal shadows in successive roentgenograms increased in density and size attaining greatest proportions in a film taken at the end of the 1st month. The shadows in films taken during the 2nd month were smaller. No signs of disease were found in any of the chest films taken after the 5th month. Similarly no evidence of disease was found in the roentgenograms of the excised lungs. At necropsy the lungs appeared natural. They were uniformily pink and smooth. They responded readily and satisfactorily to inflation. The paratracheal lymph nodes were slightly larger than usual, soft and gray. Ten large sections of the lungs were examined. No tubercles were found in any of the sections. The only abnormal features noted were the following: Some of the interalveolar septa of the left lower lobe contained an unusual amount of fibrous tissue and a few large mononuclear leucocytes. In places the pulmonary lymphoid tissue was hyperplastic. There were a few large mononuclear leucocytes in some of the hyperplastic lymph follicles of the left lower lobe. The reticular and lymphoid elements of the paratracheal lymph nodes were hyperplastic and hypertrophic. (Some of the roentgenological and pathological findings of rabbit 84 are illustrated in plate IX.)

The shadows in the chest roentgenograms of the rabbit described above were comparable in appearance and behavior to those in the chest roentgenograms of the majority of the animals in which there were no complications. Consequently it is reasonable to assume that the lesions of this animal were at different stages similar to those of other animals

which were killed. Undoubtedly there were at an early stage areas of tuberculous pneumonia with caseous foci in the left lung of this animal. Healing by resolution, nevertheless, took place. An analysis of the necropsy findings of the 16 rabbits killed after the 6th month showed that complete resolution took place in 4 cases. Healing of tuberculous lesions by resolution, is, therefore, a not uncommon occurrence.

DISCUSSION AND SUMMARY

Reinfection experimental pulmonary tuberculosis, comparable in many ways to pulmonary tuberculosis in adults, has been produced in rabbits. This was accomplished by injecting the animals in the groin with avirulent tubercle bacilli and subsequently injecting them intratracheally with measured quantities of virulent tubercle bacilli. Each animal was injected intratracheally with 1 mgm. of virulent human tubercle bacilli (strain H37, Saranac Laboratory).

The rabbits appeared ill for a period of 1 to 2 weeks following the intratracheal injection. They refused to eat. Many had fever. Subsequently most of the animals recovered, ate well and grew as rapidly as healthy control animals.

The roentgenological findings of the rabbits with reinfection experimental pulmonary tuberculosis differed from those of the rabbits with primary experimental pulmonary tuberculosis in that abnormal shadows appeared in the chest roentgenograms sooner, attained greatest size earlier and began to recede sooner. Abnormal shadows were regularly found in chest roentgenograms taken at the end of the 1st day following the intratracheal injection. The shadows were usually largest in films made during the 2nd week. As a rule films taken in the latter part of the 1st month or the early part of the 2nd month contained somewhat smaller shadows. The roentgenological findings of the two groups of animals also differed in that a larger number of the roentgenograms of the excised lungs of the rabbits with reinfection experimental pulmonary tuberculosis contained signs of cavity. Areas of rarefaction or circular shadows were found in the roentgenograms of the excised lungs of 10 of the 29 rabbits killed after the 2nd week.

The roentgenological findings of the two groups were similar in two important respects, namely, the shadows cast by progressive lesions and retrogressive lesions were comparable in many instances. Even the roentgenograms of the excised lungs, which sometimes revealed evidence

of disease when the chest roentgenograms contained no abnormal shadows, frequently failed to disclose the nature of the disease.

Finally, no shadow or combination of shadows was found in the chest roentgenograms or the roentgenograms of the excised lungs of the rabbits which served to distinguish the lesions of reinfection experimental pulmonary tuberculosis from those of primary experimental pulmonary tuberculosis.

The pulmonary lesions of the reinfected rabbits differed from those of the primarily infected animals in that they developed more rapidly, usually contained larger caseous foci, frequently underwent cavitation in the early stages and showed earlier signs of healing by organization and resolution. The lungs of successive rabbits killed between the 1st and the 12th days showed areas of tuberculous pneumonia in a state of red hepatization, then in a state of gray hepatization, and finally in a state of gray consolidation with multiple caseous foci. Complications, such as pleural effusion, miliary dissemination and cavitation, occurred in some of the rabbits during the 2nd week. An analysis showed that 7 of the 29 rabbits killed after the 2nd week had pulmonary cavities. These animals were killed at intervals such that the cavities, with one or two exceptions, showed successive stages of healing. Only one of the 7 rabbits with cavities had an extension of the disease. The lungs of the other rabbits killed after the 2nd week showed in a striking manner successive stages in the healing of areas of tuberculous pneumonia. Only minute residual lesions were found in the lungs of three-quarters of the rabbits killed after the 6th month. These observations indicate that large areas of tuberculous pneumonia, which undoubtedly contain caseous foci, frequently heal by resolution. Finally, we should like to call attention to the striking resemblance between reinfection pulmonary tuberculosis produced experimentally in rabbits and clinical pulmonary tuberculosis in adult human subjects.

REFERENCES

BALDWIN, E. R., AND GARDNER, L. U.: Amer. Rev. Tuberc., 1921, v, 429.
PHILIBERT, A., AND CORDEY, F.: Ann. Méd., 1925, xvii, 5.
SOPER, W. B., SAMPSON, H. L., AND HASKINS, C. H.: Amer. Rev. Tuberc., 1927, xv, 88.

FIGURES

PLATE I

Rabbits 73 & 74

A. P. A. film at 24 hours. Abnormal shadows, left lung field.

B. P. A. film at 48 hours. Abnormal shadows similar to those at 24 hours.

C. Film of excised lungs. Extensive shadows, left lung field.

D. Film of excised lungs. Extensive shadows, left lung field.

E. Photograph of section. Area of pneumonia in state of red hepatization.

F. Photograph of section. Area of pneumonia in state of gray hepatization.

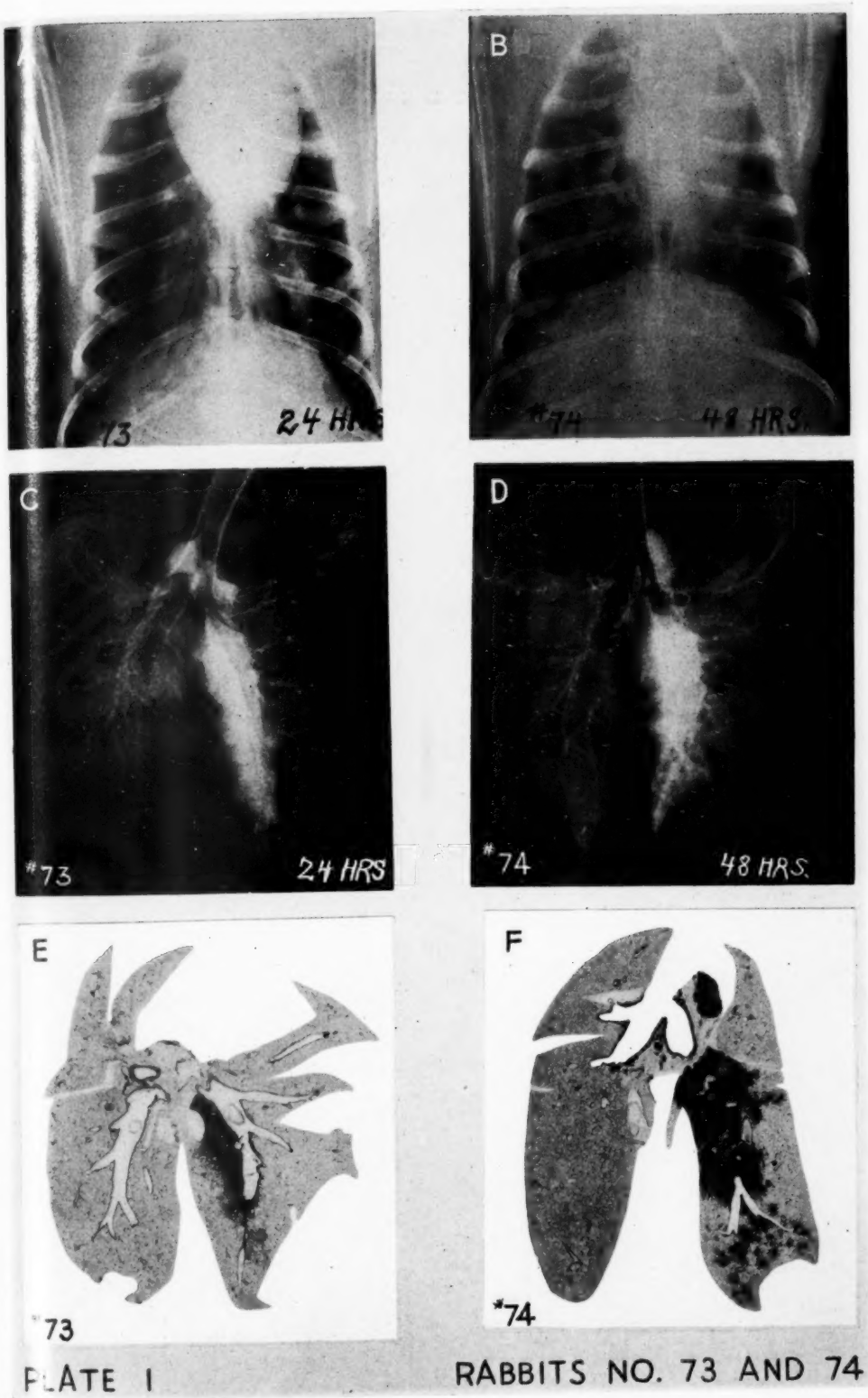


PLATE I RABBITS NO. 73 AND 74

PLATE II

Rabbit 77

A. Film at 4 days. Homogeneous shadow with indefinite margins.

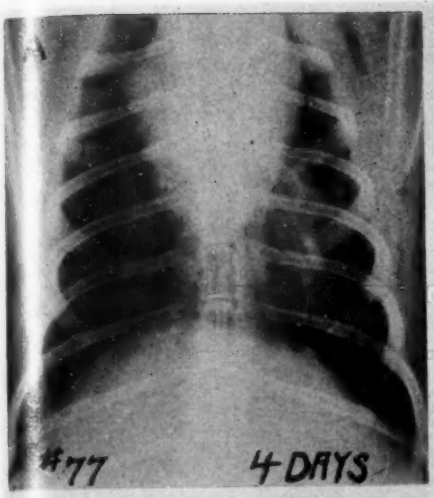
B. Film at 6 days. Homogeneous shadow with indefinite margins.

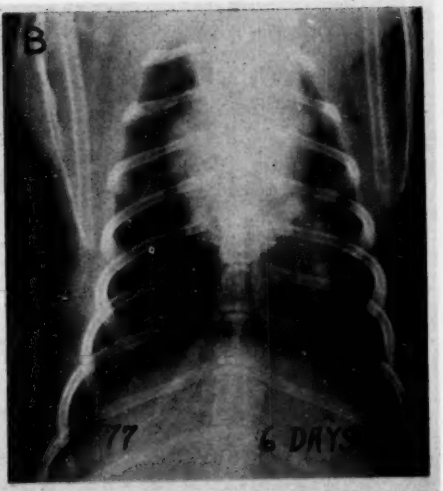
C. Film of excised lungs at 8 days. Homogeneous shadow with indefinite and definite margins.

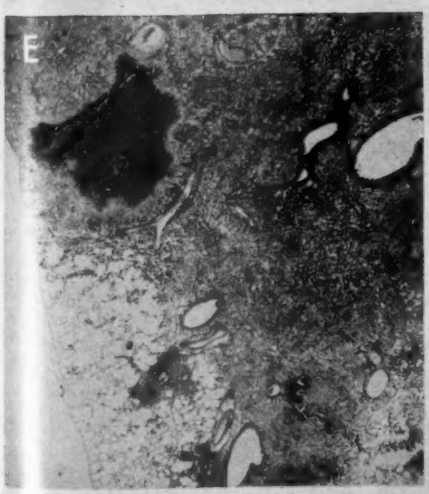
D. Photograph of section. Areas of tuberculous pneumonia.

E. Large caseous focus in area of consolidation. ×8.

F. Cellular infiltration and destruction at periphery of a caseous focus. ×400.







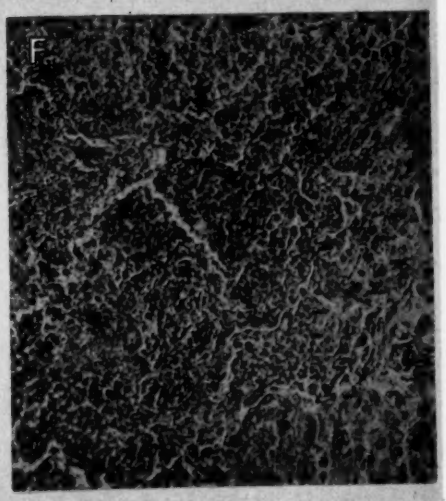


PLATE II

RABBIT NO. 77

PLATE III

Rabbits 123, 273 & 124

A. Film of excised lungs at 2 weeks. Homogeneous shadow with two rarefied areas.

B. Photographs of sections. Extensive area of tuberculous pneumonia; cavity of recent origin.

C. P. A. film at 8 days. Large homogeneous shadow, left lung field.

D. Photograph of section. Extensive area of tuberculous pneumonia and pleurisy, left lung. Isolated tubercles, right lung.

E. Film of excised lungs at $2\frac{1}{7}$ weeks. Mottled shadows left lung field and miliary shadows both lung fields.

F. Photograph of section. Areas of tuberculous pneumonia, left lung. Miliary tubercles, both lungs.

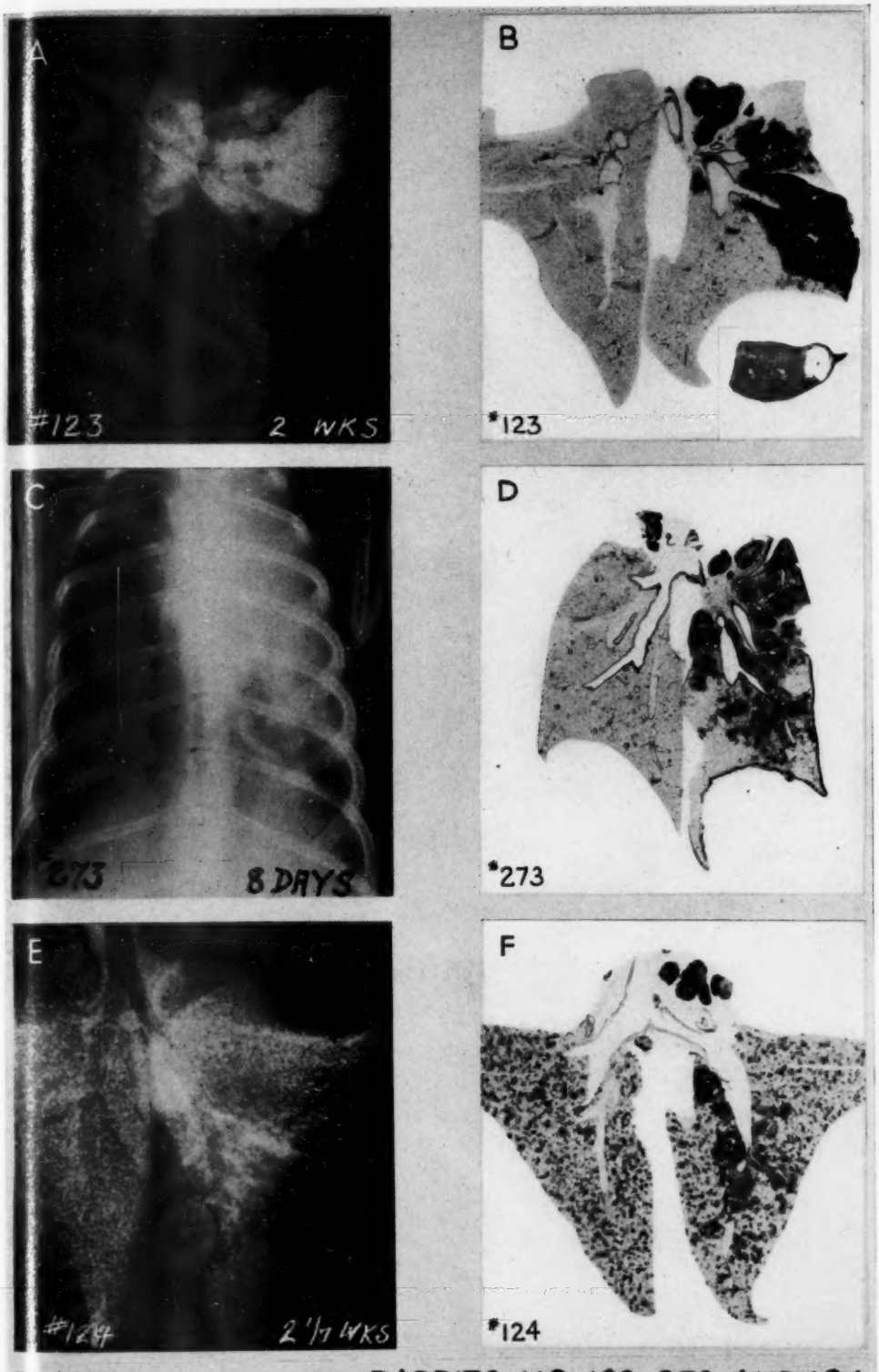


PLATE III RABBITS NO. 123, 273, AND 124

PLATE IV

Rabbit 45

A. Film at $8\frac{3}{7}$ weeks. Homogeneous shadows with indefinite margins.

B. Film at $14\frac{3}{7}$ weeks. Abnormal shadows smaller and denser.

C. Film of excised lungs. Coarse mottled shadows stippled with minute dense shadows and signs of cavity.

D. Photograph of section. Multiple fibrocaseous lesions and cavity.

E. Fibrocaseous lesions adjoining cavity wall. ×6.

F. Minute calcareous deposit in fibrocaseous lesion. ×100.

PLATE IV RABBIT NO. 45

PLATE V

Rabbit 47

A. Film at $4\frac{6}{7}$ weeks. Homogeneous shadows with indefinite margins.

B. Film at $12\frac{3}{4}$ weeks. Shadows similar but smaller.

C. Film at $21\frac{6}{7}$ weeks. No abnormal shadows.

D. Film of excised lungs. Faint homogeneous shadows and oval shadow indicative of cavity.

E. Photograph of section. Fibrocaseous lesions adjacent to main bronchus of left lower lobe and cavity similar to that of rabbit 45.

F. Loss of elastic tissue in wall of main bronchus (in upper left hand corner). Elastic-tissue stain. ×90.

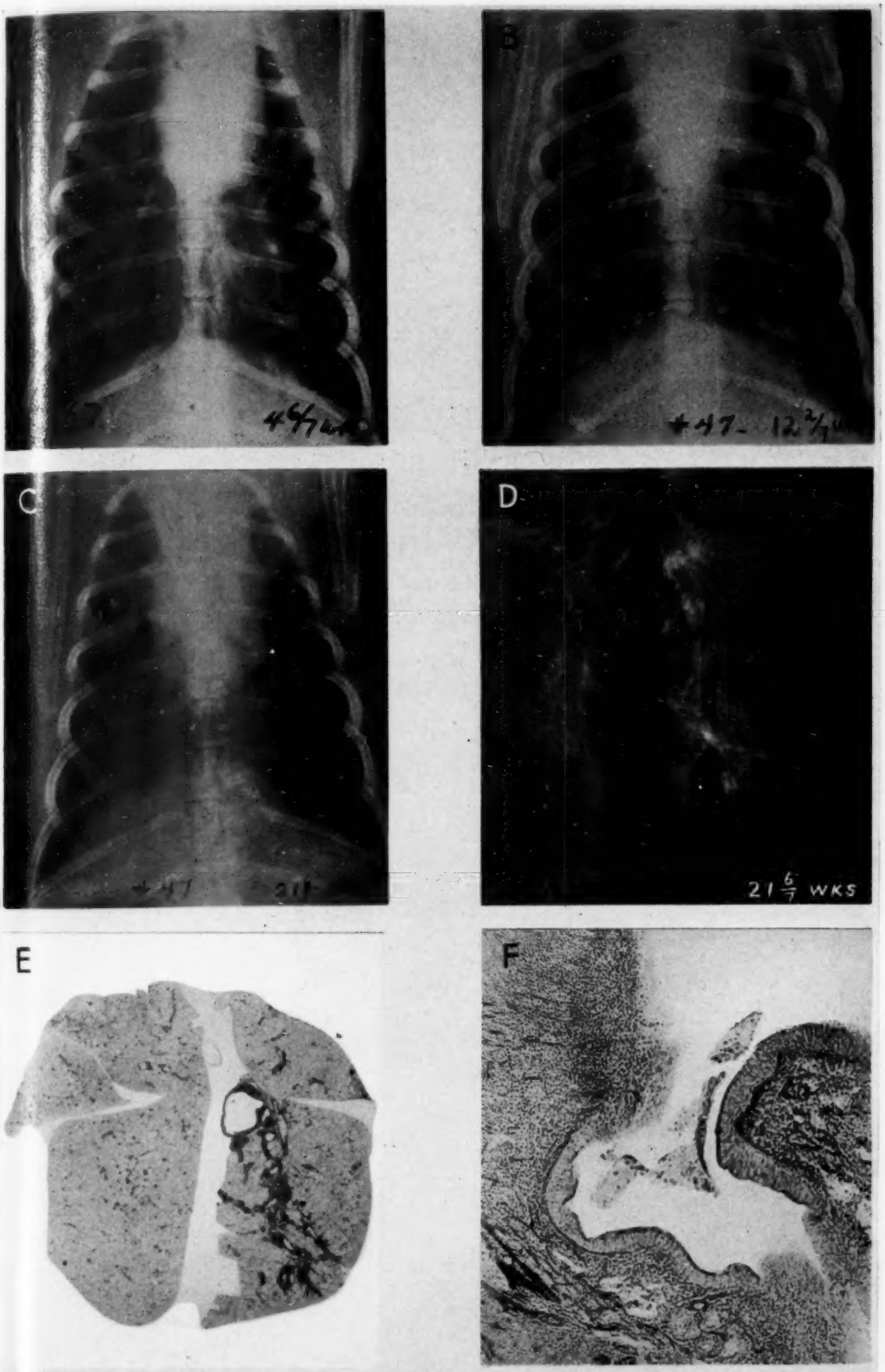


PLATE V

RABBIT NO. 47

PLATE VI

Rabbit 82

A. Film at $5\frac{4}{7}$ weeks. Homogeneous shadows with definite and indefinite margins.

B. Film at $20\frac{1}{7}$ weeks. No abnormal shadows.

C. Film at $102\frac{5}{7}$ weeks. No abnormal shadows.

D. Film of excised lungs. Outline of left upper lobe, large; of left lower lobe, small. Circular shadow in left lower lung field suggestive of cavity.

E. Photograph of section. Emphysematous left upper lobe and small left lower lobe containing dilated bronchi and two minute cavities.

F. Portion of wall of one dilated bronchus, areas of fibrosis and emphysema, and minute cavity containing caseous material. ×15.

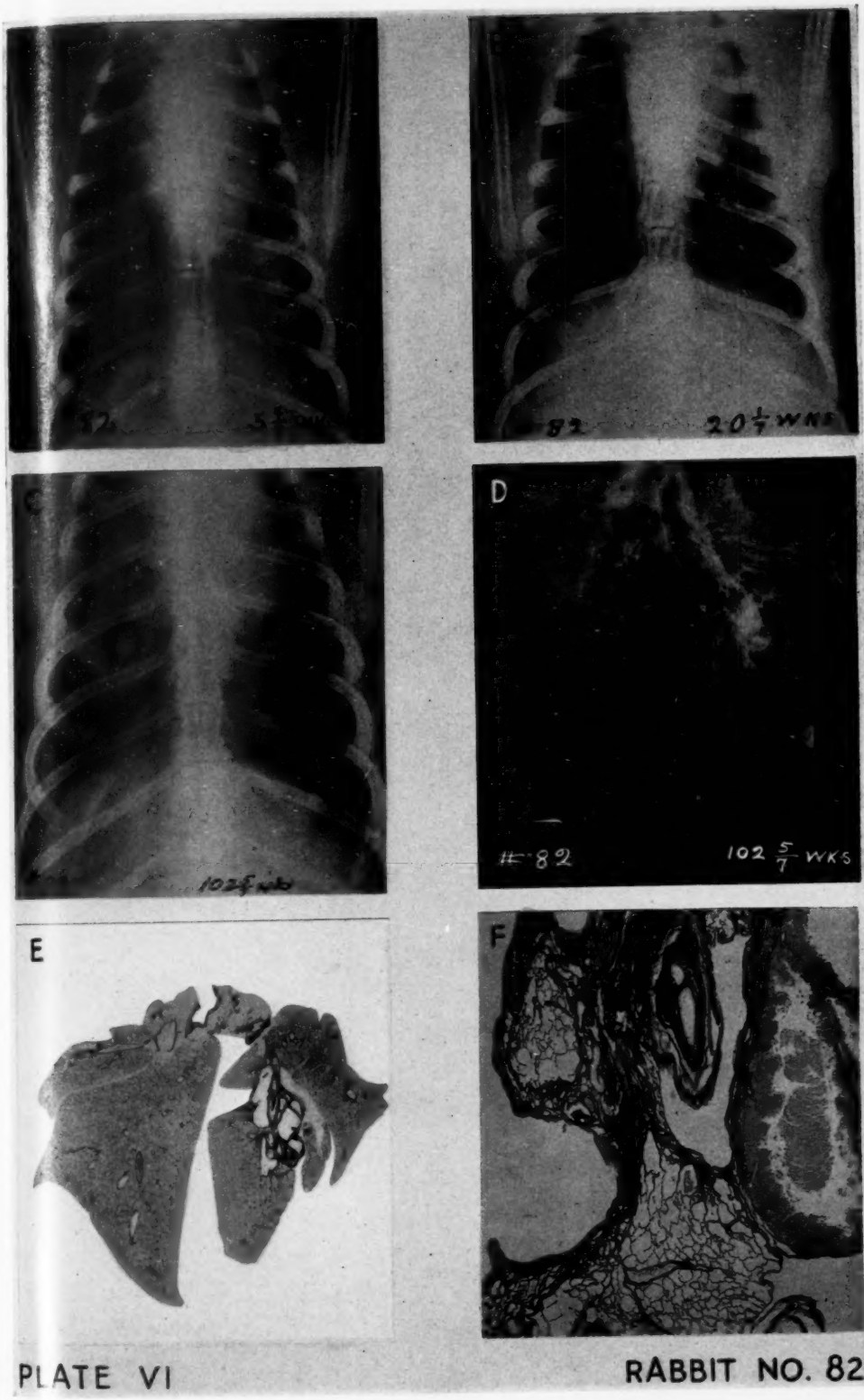


PLATE VI

RABBIT NO. 82

PLATE VII

Rabbit 125

A. Film at 2 weeks. Abnormal shadows, left lung field.

B. Film at $2\frac{6}{7}$ weeks. Abnormal shadows similar.

C. Film of excised lungs. Homogeneous and mottled shadows.

D. Photograph of section. Large and small areas of tuberculous pneumonia.

E. Caseous foci in an area of tuberculous pneumonia. ×8.

F. Fibroblasts, fibrous tissue and giant cells near a caseous focus. ×400.

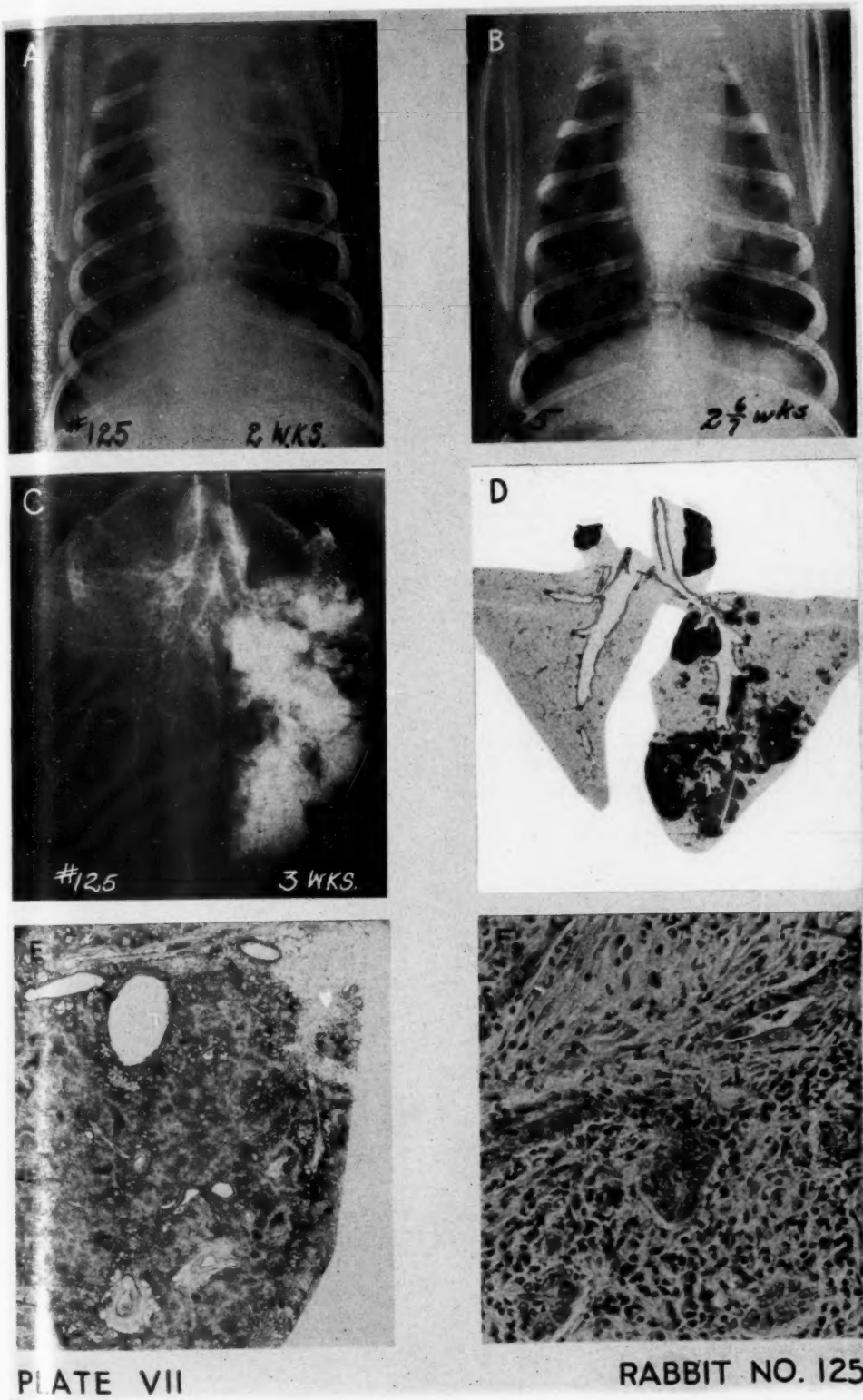


PLATE VII

RABBIT NO. 125

PLATE VIII

Rabbits 136 & 137

A. Film at $3\frac{3}{7}$ weeks. Faint homogeneous shadows, left lung field.

B. Film at 23 days. Faint homogeneous shadow, left lung field.

C. Film at $33\frac{4}{7}$ weeks. No abnormal shadows.

D. Film at $34\frac{1}{7}$ weeks. No abnormal shadows.

E. Film of excised lungs after injection with lipiodol. Small left lung field. Signs of constriction of main bronchus of left lower lobe.

F. Film of excised lungs. Small left lung field. Isolated discrete shadows suggestive of calcareous deposits.

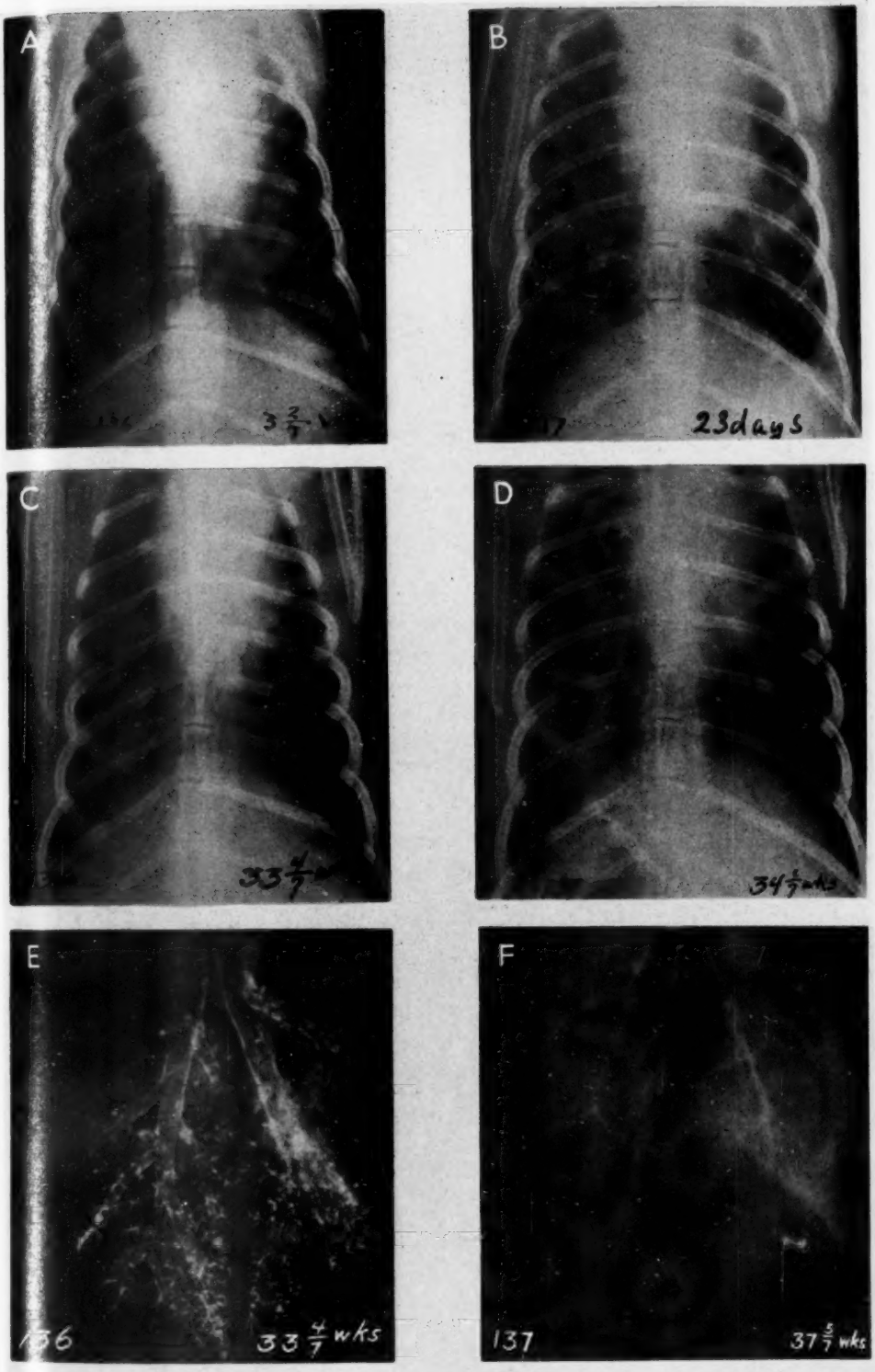


PLATE VIII RABBITS NO. 136 AND 137

PLATE IX

Rabbit 84

A. Film at 3 days. Homogeneous shadow with indefinite margins, left lung field.

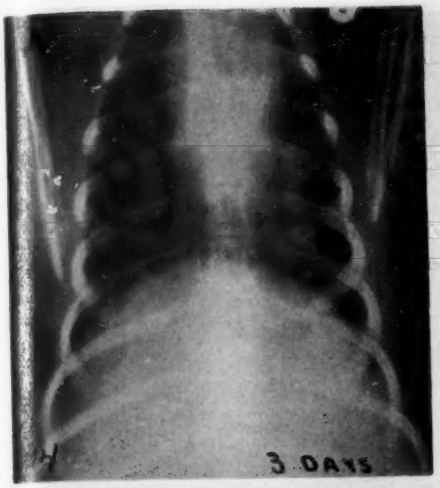
B. Film at $5\frac{4}{7}$ weeks. Extensive irregular shadows, left lung field.

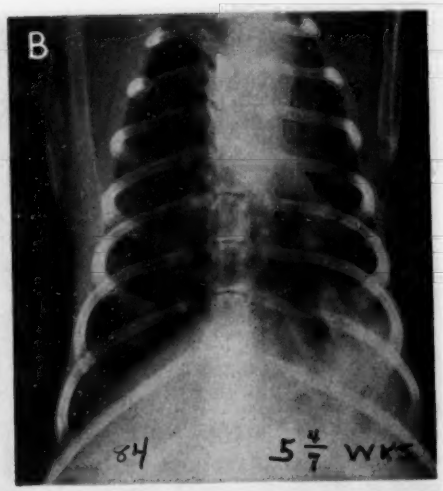
C. Film at $17\frac{1}{7}$ weeks. Faint homogeneous shadows, left lung field.

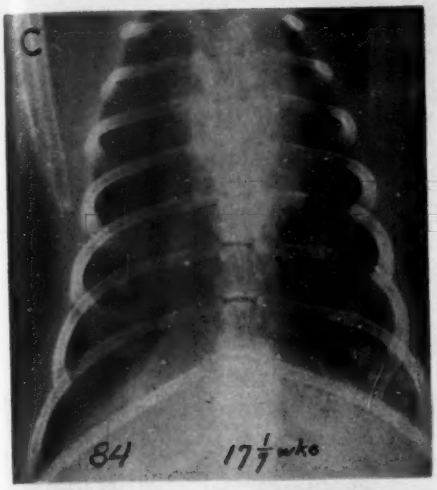
D. Film at $56\frac{3}{7}$ weeks. No abnormal shadows.

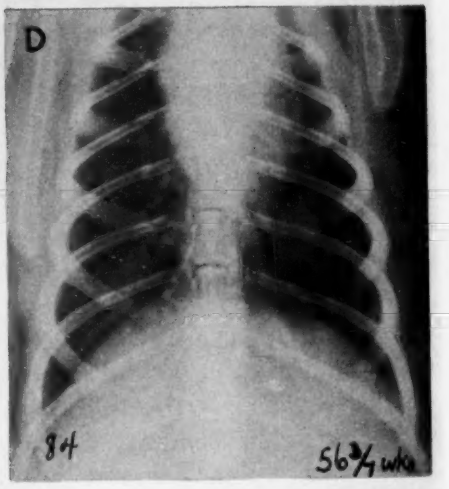
E. Photograph of section. No macroscopic lesions.

F. Portion of left lower lobe. Only abnormally thick septa. $\times 60$.









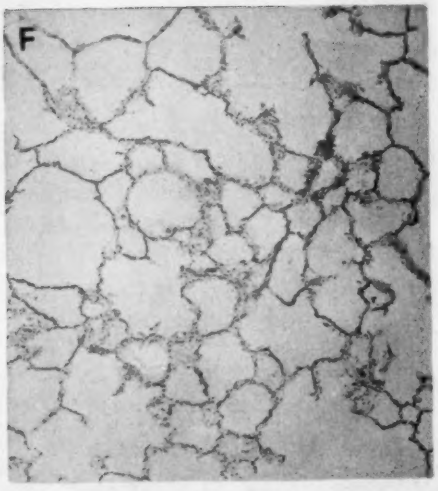


PLATE IX

RABBIT NO. 84

ATYPICAL ACID-FAST MICROÖRGANISMS

III. Chromogenic Acid-Fast Bacilli from Human Beings[1,2]

MAX PINNER

During the last three years a number of pigmented acid-fast bacilli appeared on media seeded with various types of human material in the attempt to isolate tubercle bacilli. At first they were thought to be contaminators, in the sense that they were not derived from the material under examination, but from outside sources, such as water, chemicals, media or air. Numerous attempts were made to culture some such organisms from the suspected sources, but they failed completely. Yellow colonies of acid-fast bacilli were obtained from tap-water and from the scrapings of cold-water faucets. But, as will be explained later, these organisms whose frequent occurrence is well known since Brem's work (1) are significantly different from the group of bacilli to be discussed here. Furthermore, tap-water was, of course, not used in our culture work. These microörganisms occurred in much less than 1 per cent of our cultures for tubercle bacilli; this constitutes a further argument against their derivation from anything else but the material examined by cultural methods.

The various strains seem to belong to a fairly well defined group. But the apparent differences between individual strains are sufficiently great to warrant some special discussion.

DERIVATION OF STRAINS

The group comprises at the present 15 strains, as follows:

D: From sputum of a man with an old fibrotic tuberculosis of the lung; the sputum contained at the same time typical human tubercle bacilli.
Cr: From the urine of a woman with a chronic pyelonephritis, the aetiology of which remained undetermined.
Z: From the urine of a man with pulmonary tuberculosis (bacilliferous sputum) and coccidioides, but without symptoms and signs of urogenital disease.
W: From the urine of a patient with tuberculosis of one kidney and epidid-

[1] From the Laboratory of the Desert Sanatorium and Institute of Research, Tucson, Arizona.

[2] Presented in part before the Pathological Section of the thirty-first annual meeting of the National Tuberculosis Association, Saranac Lake, New York, June 25, 1935.

ymis; typical human tubercle bacilli were simultaneously isolated from the urine.

S: From the urine of a woman suffering from scleroderma, infectious arthritis and pulmonary fibrosis, with the aetiology of the latter unknown. The patient had no symptoms or signs of urogenital disease.

Sm: From the gastric lavage of a young girl with pulmonary tuberculosis; a few months previously typical tubercle bacilli had been demonstrated in the sputum of this patient.

Mc: From the urine of a woman who had repeated small haematuria, slight nocturia and pain on urination; all symptoms disappeared in a short time. The urine specimen from which the culture was grown showed acid-fast bacilli in the smear from the sediment and a moderate number of red cells; but it failed to produce tuberculosis in a guinea pig.

B: From the stool of a woman who died a few weeks later of sarcoma of the mediastinal lymph nodes. At autopsy no lesions were found besides the tumor, with the exception of a chalky lymph node over the bifurcation of the left iliac vein and an ancient tuberculosis of a tracheobronchial lymph node. From neither of these lesions could acid-fast bacilli be isolated by animal inoculation or by culture.

No: From the sputum of a patient with pulmonary tuberculosis; this strain was isolated in the laboratory of the Maybury Sanatorium, Northville, Michigan (Dr. H. S. Willis).

M: From the blood of a patient with pulmonary tuberculosis.

Ne: Ibid.

P: Ibid.

F: From the pus of a patient with tuberculosis of the hip-joint.

(The last four strains were isolated in the laboratory of the Board of Health of Detroit (Dr. J. F. Norton).)

Gr: From the urine of a patient with pulmonary tuberculosis whose sputum contained typical tubercle bacilli.

Ct: From the urine of a patient with arrested pulmonary tuberculosis with negative sputum and with suspected tuberculous prostatitis.

GENERAL BACTERIOLOGICAL CHARACTERISTICS

1: Individual morphology: All these 15 strains are acid-fast, gram-positive, nonmotile, non-spore-bearing rods. After staining with hot carbol-fuchsin solution, they retain most of the color following decolorizing with 3 per cent hydrochloric acid in 70 per cent alcohol for 24 hours. They are quite polymorphous. Particularly in older colonies, many short, thick rods and free granules are seen. The majority of the organisms closely resemble tubercle bacilli, but most of them are somewhat

larger, and particularly less slender. Intrabacillary granules occur, but are not frequent. Young colonies contain, as a rule, many acid-fast granules and non-acid-fast rods.

2: Growth: They grow best on egg and potato media. Growth on glycerol-agar is scant and slow, and absent on glycerol-free-agar. In glycerol-broth some strains do not grow at all, while others slowly form thick pellicles and a somewhat slimy sediment; growth on Kirchner's serum-broth (11) is the same. Malachite-green and gentian-violet in the usual concentration do not retard growth. No growth was obtained on gelatine. At incubator temperature, visible colony-formation occurs within three or four days; maximum development requires two to four weeks. At room temperature, growth is somewhat slower than at 37°.

3: Appearance of colonies: Mature colonies are hemispherical, perfectly smooth and shiny, and creamy to viscous in consistence. Colonies with rough characteristics were never seen. The colonies are lemon-yellow to dark orange. The intensity of the pigmentation increases with the age of the colonies. Occasionally, some transplants are creamy-white, but on further transplants the original pigmentation returns sooner or later. This change is apparently not caused by the media. The colonies are readily brought into fine and even suspensions in water or saline solution. Media containing malachite-green become more or less completely decolorized as growth proceeds.

4: Pathogenicity: All strains were tested for pathogenicity in guinea pigs, and with the exception of five strains (Sm, Mc, G, Ct and No) they were all tested for pathogenicity in guinea pigs, rabbits and chickens. Small doses of bacilli did not produce any demonstrable lesions. After this fact was established, the bacilli were injected in 10-mgm. doses subcutaneously into guinea pigs, and intravenously in rabbits and chickens. Even in such large amounts, the response of the animals was far from uniform. With the very low virulence of these strains, differences in individual susceptibility became apparent to a marked degree. With tubercle bacilli of normal virulence such differences tend to be largely obscured. With due regard to the individual variations mentioned, the development of lesions in guinea pigs after subcutaneous injections of about 10 mgm. of moist bacilli, can be described as follows:

Pathologicoanatomical Characteristics

At the point of injection, a nodular subcutaneous swelling becomes palpable within three to nine days after injection. This nodule is soon transformed into an abscess, which develops in the subcutaneous tissue and not in lymph nodes. The draining lymph nodes may or may not become enlarged. The local lesion attains its maximum size in from two to three weeks; after this, it recedes slowly and it is usually no longer palpable five to seven weeks after infection. When the animals are killed after palpable nodes have disappeared, one finds small white subcutaneous scars which show within a slight fibrous capsule the remnants of granulomatous tissue and in the centre some inspissated pus and necrotic material.

At the height of the development, the abscess is embedded in the abdominal musculature. Fistulae rupturing through the skin occur only exceptionally. Small perforations into the peritoneal cavity are frequent,—an occurrence that is extremely rare after the subcutaneous injections of true tubercle bacilli.

The lesions in the internal organs depend largely on the presence of these peritoneal perforations. The latter seem to occur quite early and are but rarely patent at the height of the disease, but their previous patency is frequently deducible from the distribution of the internal lesions. Within one or two weeks after the infection, some animals show a serous peritonitis, with large numbers of acid-fast bacilli in the effusion, and an occasional animal dies at this stage. Later on, the characteristic lesions are as follows: The omentum is rolled up and thickened, lying as a pale cream-colored, sausage-shaped mass along the major curvature of the stomach. The spleen, normal in size, or slightly enlarged, shows some fibrino-fibrous tags, which in later stages form perilienal fibrous adhesions. Similar deposits may be present on the hepatic capsule. In a few instances there was abscess-formation in one or both testicles with marked periorchitic adhesions. Within the parenchyma of the spleen and the liver, a few white, sharply circumscribed nodules of 0.5 to 2 mm. in diameter may or may not be found. Similar but usually smaller lesions are seen in the lungs of some animals. The lymph nodes are swollen and at times suppurating in about half the animals. The superficial inguinal lymph nodes at the side of the injection are frequently, but not always, involved. The lumbar lymph nodes show macroscopical lesions more frequently than the deep inguinals. Mesenteric lymph

nodes and periportal nodes are occasionally involved, but macroscopical changes in the nodes at the pulmonary roots are rare.

In rabbits, following intravenous injections of 10 mgm., submiliary dense and hard nodules are produced by only two strains (Cr and M) in the lungs.

In chickens, similar lesions and miliary necroses occur in the kidneys, spleen, liver and lung, following intravenous injections of strains Cr, Z, M, B, F and S.

Histological Characteristics

In the earliest stage, the local lesions consist of granulomatous tissue with many large histiocytes, some typical epithelioid cells, very few giant cells, and few polymorphonuclear cells (figure 1). The striking characteristics of these granulomata, as compared with young tubercles, is the extreme polymorphism of the cells, their tendency to invade surrounding tissue, such as muscles (figure 2) and the mammary gland, and the enormous number of acid-fast bacilli they contain. Two to four weeks after infection, the local lesion shows a central abscess which is surrounded by highly polymorphous granulomatous tissue. Later on, the pus becomes inspissated and the granulomatous capsule is transformed into hyaline connective tissue. The lesions in the lymph nodes are quite similar to those in the subcutaneous tissue (figure 3).

The lesions in the internal organs show essentially the same developmental cycle as do the local lesions, but they do not grow to the same size. Parenchymal foci hardly ever are larger than 2 mm. in diameter and they

Fig. 1. Section through local lesion at site of injection. Guinea pig killed 14 days after injection. This section shows the polymorphous character of the granulation tissue.

Fig. 2. Section through local lesion at site of injection. Guinea pig killed 19 days after injection with strain S. Note the invasion of the muscular tissue by the inflammatory process.

Fig. 3. Section of a sacral lymph node. Guinea pig killed 15 days after injection with Strain Cr. This photomicrograph shows the replacement of the lymphoid tissue by a highly polymorphous granulomatous tissue.

Fig. 4. Section of liver of a guinea pig, killed 71 days after infection with strain M. Note the four submiliary granulomata.

Fig. 5. Section of the lung of a guinea pig, killed 35 days after infection with strain D. Marked interstitial cellular infiltration.

Fig. 6. Section of lung of a guinea pig killed 25 days following infection with strain B. One miliary tubercular focus with a giant cell and irregular cellular infiltration of the interstitial tissue.

Fig. 7. Section of liver of a guinea pig that received two injections of strain Cr at 29-day interval and that was killed 40 days after the first injection. There is an abscess surrounded by granulation tissue.

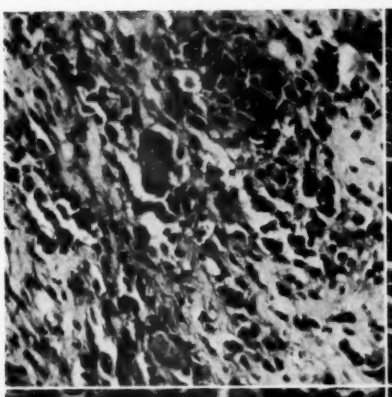


FIG. 1

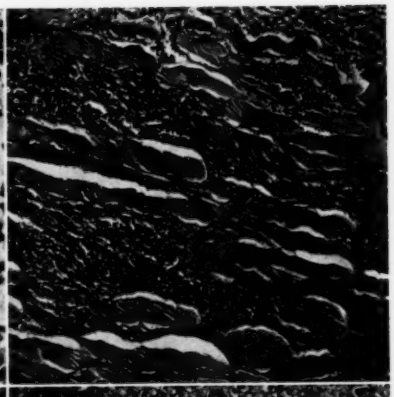


FIG. 2

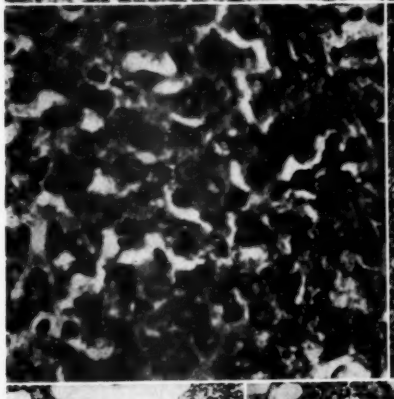


FIG. 3

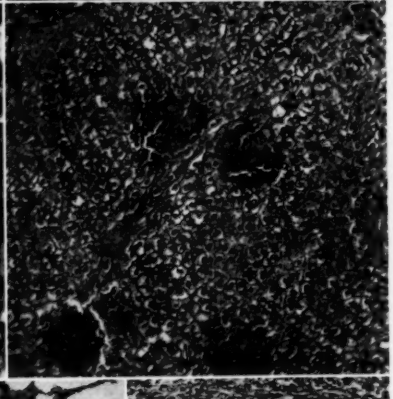


FIG. 4

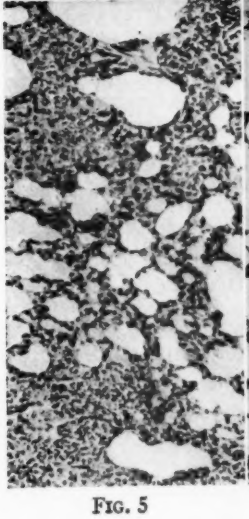


FIG. 5

FIG. 6

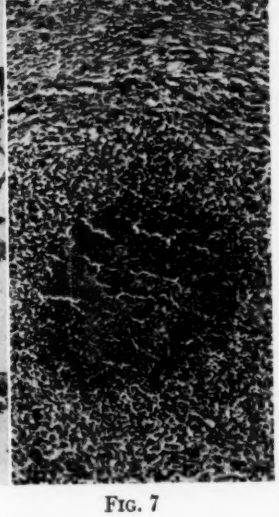


FIG. 7

are so scarcely distributed that coalescence is extremely rare. In macroscopically normal livers, spleens and lungs, minute granulomata are found quite frequently, particularly late in the disease (figure 4), as is true occasionally of lymph nodes. In the lung, abscess-formation is never found; instead the granulomata contain many more lymphocytic cells than in other organs; the foci are frequently not as round as those in other organs, but spread more along the interstitial structures. The late result in the lung is a more or less diffuse, chronic interstitial inflammatory tissue, leading to thickening of the alveolar walls (figures 5 & 6). The whole process is strictly interstitial; exudative, intraälveolar processes are absent. Acid-fast bacilli in these lesions are very rare. The kidneys never show lesions, although bacilli were recovered from the postmortem urine in several instances. The final fate of parenchymal lesions is absorption; cicatrization, such as occurs in the local foci, is rare.

Throughout the course of development, caseation is absent, while in some of the larger lesions suppuration is frequent.

The lesions in rabbits and chickens are practically all of microscopical size. Histologically, they are granulomata, similar to those found in guinea-pigs, and small necroses without any apparent reaction of the tissue. The granulomata contain very few acid-fast rods, while the necroses frequently swarm with rods and granules.

5: Virulence: In regard to virulence the strains can be grouped roughly into three groups:

1: Strains that regularly produce intraperitoneal and parenchymal lesions (D, Cr, M, S).
2: Strains that produce such lesions in some of the animals (Z, Ne, B, W, P).
3: Strains that produce as a rule only local lesions (Sm, F, No).

In order to find out whether the virulence of these bacilli could be enhanced, direct and indirect animal transfers were done with strains B, Cr, Ne, D, Z, Mu. In the direct transfer experiments, all the involved organs of an infected animal were triturated with saline solution and injected subcutaneously into a normal guinea pig. The indirect transfers followed the schedule: Infected organs—culture—animal, etc. The direct transfer produced characteristic lesions of decreasing severity up to and including the second generation with strains B and Z, the third with strain Ne, the fourth with strains Cr and Mu, and the fifth with

strain D. Indirect transfer could be carried practically *ad lib.* if the animals were killed soon enough after infection. Of all animals, cultures were prepared at autopsy from all involved organs, and usually from the spleen. Up to two or three weeks following the last injection, cultures of the injected organisms were obtained in the vast majority. As the period between infection and autopsy increased, positive cultures became progressively rarer. This coincides with the anatomical and histological evidence of healing. With some exceptions to be discussed later on, neither direct nor indirect animal transfers enhanced the virulence of these strains.

6: Reinfection: Several series of animals received two injections, two to four weeks apart in order to test the allergic response. With most strains, the second injection caused a soft, oedematous swelling without distinct redness at the site of reinjection within 24 hours. This swelling developed into a hard nodule, then into an abscess and then receded, all approximately twice as fast as in the case of a primary infection. In spite of this apparent allergic response, reinjected animals showed pathological lesions in the internal organs more extensively and more regularly than animals that had received only one injection. The type and general pattern of the lesions were the same in both groups of animals, but abscess-formation was more pronounced in the reinjected groups. Figure 7 shows the type of abscess formation frequently seen in the reinjected animals, while figure 3 is representative of the granulomatous lesions in animals that received only one injection. The most striking difference between animals injected once and those injected twice is quantitative and not qualitative. The total amount of bacilli administered to reinjected animals was roughly the same as that given to animals receiving but one injection.

After the difference between once- and twice-injected animals was established, several groups of guinea pigs received up to 12 subcutaneous injections of 0.1 mgm. each at intervals of 4 to 6 days. These animals developed, as a rule, only small subcutaneous abscesses and no internal lesions.

Guinea pigs, infected with the various strains, react in the typical manner to intracutaneous injections of Old Tuberculin (1:10) and to culture filtrates of the homologous strain. As mentioned above, some strains could not be grown on glycerol-broth; in these strains, bacterial suspensions were used for the intracutaneous tests instead of culture

filtrates. Skin allergy to tuberculin and to the homologous strain was present from the tenth day after infection for a period of about two weeks; after this time it decreased markedly. Tuberculous guinea pigs reacted

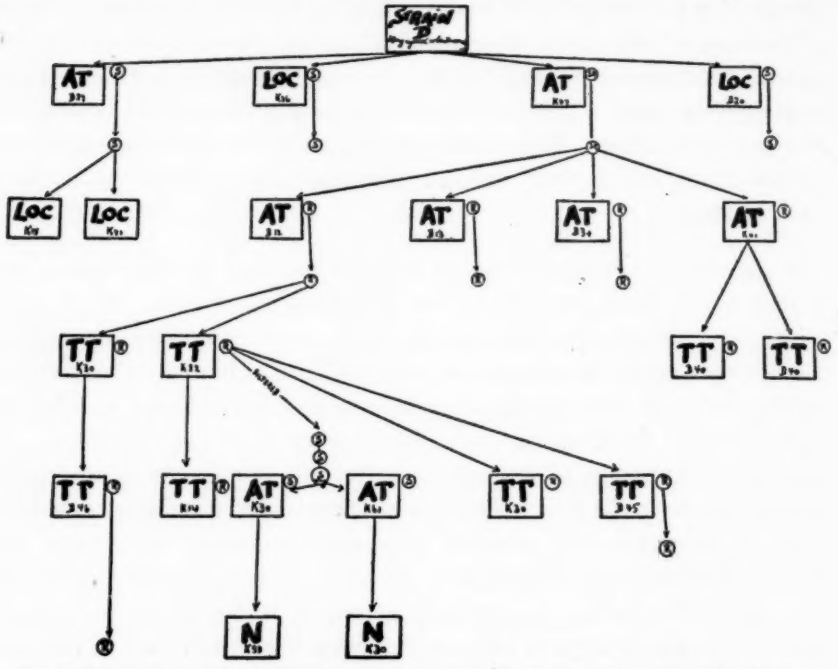


Fig. 8. Diagram showing increase in virulence of strain D. Explanation of symbols:
□ = guinea pig
AT = atypical tuberculosis
Loc = local lesion only
TT = typical inoculation tuberculosis
N = no lesions attributable to infection
⑤ = smooth chromogenic colonies isolated
⑱ = typical tubercle bacilli isolated
Kx = killed x days after infection
Dx = died x days after infection
Arrow pointing from square to square = direct animal transfer
Arrow pointing from circle to square = injection of culture
Arrow pointing from circle to circle = test tube transfer.

to culture filtrates and to bacillary suspensions of these strains in approximately the same way as to tuberculin.

7: Increase in virulence: It was mentioned above that some exceptions occurred to the rule of fixed virulence of these strains. Strain D and strain Cr showed a spectacular increase in virulence. Figure 8 repre-

sents the experiment in which strain D showed an apparent transformation.

All guinea pigs in the second horizontal row showed the type of lesions characteristically produced by these chromogenic strains (atypical tuberculosis). Four of the six animals, all injected with the same strain that showed some rough characteristics but was fully chromogenic, yielded rough colonies. These first rough colonies had the colony characteristics of tubercle bacilli, but they were considerably more pigmented than

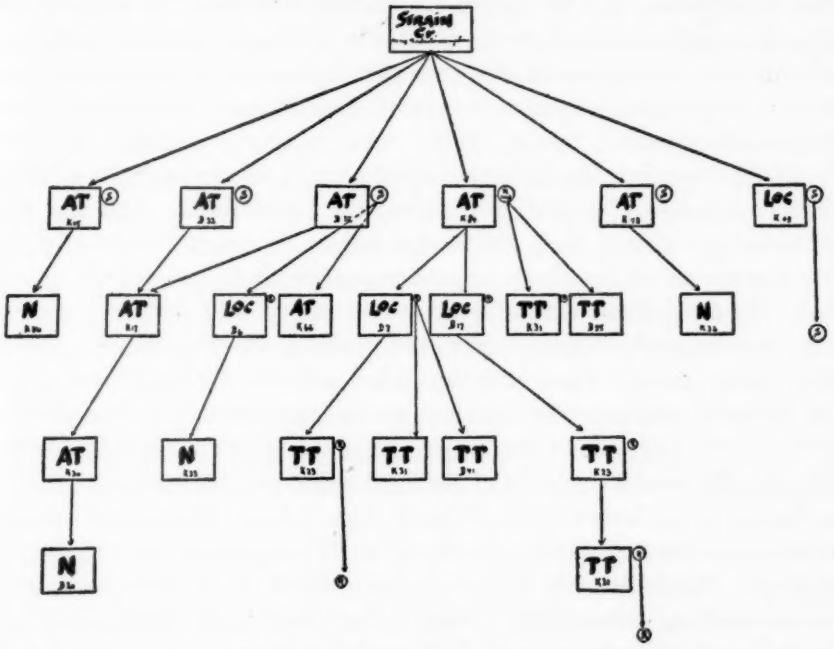


Fig. 9. Diagram showing increase in virulence of strain Cr. Explanation of symbols is same as for fig. 8.

tubercle bacilli are as a rule. The animals injected with this modified strain or with the organs of animals from which this strain was derived all developed typical inoculation tuberculosis and the bacilli isolated from them are in all regards undistinguishable from typical human tubercle bacilli. One strain was filtered through filter paper in an attempt to obtain isolated colonies, and from the culture of the filtrate one colony was obtained that had all the characteristics of the original strain.

A similar series of experiments is shown in figure 9 with strain Cr.

When these observations were made the first impulse was to disregard them as due probably to contamination with tubercle bacilli. Theoretically, such a contamination may occur either in the material used for injection or in an animal due to spontaneous infection. Neither possibility can be excluded with absolute certainty. As to spontaneous infection it may be mentioned that not a single instance of it has occurred in our animals during the last four years. Furthermore, inoculation tuberculosis can be definitely differentiated from a spontaneous alimentary or respiratory infection by the local progressive lesion at the site of infection. It is granted that this local lesion may be absent following minimal infections, but, when it is present, as it was in our animals, it is diagnostic beyond a doubt. If by some unknown accident tubercle bacilli had been introduced in the experiment, it should be expected that the first animal so infected show a clear-cut tuberculosis. This was not the case; the change from the benign lesions produced by the original strain was slow and gradual. In the case of strain D, rough bacilli were isolated from animals with atypical tuberculosis, and only the next generation of animals showed typical tuberculosis. With strain Cr conditions were similar. Even at a time when so-called "typical inoculation tuberculosis" was produced by these two strains, the lesions showed two characteristics typical of the original strains and not of tubercle bacilli, namely, the invasive growth of the local lesion and the striking number of bacilli in the lesions. Particularly, the former characteristic seems rather important; it did not disappear in several generations of infected animals. These findings seem to justify doubt as to the question of contamination with tubercle bacilli. But, since many attempts at reproducing the enhancement of virulence failed, it cannot be asserted that actual increase in virulence occurred and that contamination was not operative.

DISCUSSION

A large number of acid-fast bacilli other than tubercle bacilli have been described by many workers. According to their habitat, the variety of strains is immense, but on strictly bacteriological criteria it is rather evident that many a strain must have been described repeatedly by different workers (Mironescu (17), Krause (13)). The classification of these strains is still as chaotic as it was in the beginning of this century. Classification as to habitat proved hopeless because acid-fast bacilli

have been isolated from almost any material that was properly scrutinized. Classification as to pathogenicity is hampered by the fact that the term "pathogenic" is nearly meaningless unless strictly defined in terms of animal species, dosage, time-interval between infection and pathological examination; and, most important of all, there is no general agreement on what constitutes disease in infected animals. If any demonstrable tissue alterations be called disease, and accordingly any organism that causes them is considered pathogenic, then, there are no apathogenic acid-fast organisms. To stipulate a minimal dosage that must produce disease, in order to admit the organism into the classification "pathogenic," is totally arbitrary. To assign the term *pathogenic* only to those microörganisms that cause progressive disease, and to exclude all those that produce self-healing lesions, would exclude a major portion of all so-called pathogenic (non-acid-fast) organisms. But such proposals are on record. A fairly clear-cut distinction can be made by establishing whether a given microörganism causes lesions, progressively or retrogressive, in serial transfers from animal to animal. If this criterium is used to differentiate between pathogenic and saprophytic acid-fact bacilli it is apparent that all non-mammalian acid-fasts belong in the saprophytic group, although it has probably never been settled whether or not some acid-fasts isolated from cold-blooded animals are, in the sense specified, pathogenic for the respective species.

The saprophytic group thus defined is still a fairly heterogeneous conglomeration of bacilli. The many strains differ in individual morphology, staining reactions, colony-formation, pigmentation, nutritional and thermic requirements, rate of growth, endotoxin (tuberculin-like substances) production, chemical composition, serological specificity, antigenic structure and in their biological activity in animal tissue. Which of the criteria mentioned may, or may not be, used in classification is questionable, since it is not known whether they are constant species characteristics or variable, depending upon environmental conditions.

In the absence of a usable established classification, the taxonomic question must be dropped, and it remains only to enumerate some of the acid-fasts previously described, that are apparently more or less similar to the organisms described in this report.

A large number of saprophytic acid-fasts produce a yellow pigment, such as the butter bacillus (Rabinowitsch (24), Petri (19)), *Mycobacterium phlei* (Moeller (18)), *M. stercusis* (Moeller (18)), acid-fast bacilli isolated from the sputum of a case of pulmonary gangrene (Rabinowitsch (25)),

a group of acid-fast bacilli isolated from leprosy in man and especially in rats (Clegg (2)), *M. lacticola* (Korn (12)), bacilli from nasal secretions (Karlinski (10)), some acid-fasts isolated from trumpets (Merten (16)). The early work on these organisms has been reviewed and summarized by Potet (23), and by Crouzon and Villaret (3). Allen Krause (13) discussed the significance of these saprophytic bacilli in 1920; and since then, little, if anything, has been added to our knowledge of this subject. More recently, Thomson (29) contributed further attempts at classification, and her "group II" has many apparent similarities to the strains reported here. The vast majority of all chromogenic saprophytic acid-fasts reported before 1910 have dry, rough colonies that, not unlike those of tubercle bacilli, are not easily suspended in saline solution. The notable exceptions to this rule are the strains isolated from human material by Rabinowitsch and by Karlinski.

In the last few years, since cultural methods have been employed more frequently in diagnostic work, and particularly since the renewed attempts at isolating tubercle bacilli from the blood, a number of authors have found atypical acid-fasts, apparently derived from human material. I (20) have mentioned such findings recently, and, since then, the following reports have come to my knowledge:

Rabinowitsch (26) cultured 262 samples of blood, and obtained 15 transplantable strains of acid-fast bacilli; of these, 7 were not tubercle bacilli, but grew in gray to yellow viscous colonies of fully acid-alcohol- and antiformin-fast rods of very low virulence for guinea pigs.

Tiedemann (30) described a similar strain, isolated from the blood of a patient with chorioretinitis. The colonies were yellow, smooth and moist. The organisms were very polymorphous and unevenly acid-fast. This strain was reported to be completely avirulent.

Popper, *et al.* (21) (22) isolated 6 strains from postmortem blood, and 6 from the blood of living patients. They produced moist, yellow colonies and were avirulent for guinea pigs.

Schwabacher (28) reported a particularly thorough study. She obtained chromogenic, saprophytic acid-fast bacilli from the blood of 6 tuberculous patients, one patient with schizophrenia, 6 tuberculous rabbits and 3 normal rabbits, from water (6 strains), from dust (3 strains) and one strain from a comedo. Some of these strains had rough, while others had smooth colony characteristics. They were all avirulent in 1.0-mgm. doses for guinea pigs.

Cummins and Williams (4) isolated a similar strain from sputum and Griffith (7) studied it bacteriologically.

Daines and Austin (5) (6) isolated three different groups of acid-fast organisms from cutaneous lesions in tuberculin-reacting cattle. Their group III resembles closely the chromogenic strains here described. Through the courtesy of Dr. Daines I received two of these cattle strains, their general bacteriological characteristics are quite similar to those of my human strains.

This enumeration suffices to show that chromogenic acid-fast bacilli occur rather frequently in human and animal tissues. This emphasizes the necessity of identifying acid-fast bacilli that may be found in diagnostically uncertain cases.

The strains, reported here, seem to cause more definite lesions in guinea pigs than do most other strains belonging in the same group. Whether this apparent difference is due to dosage or due to the fact that they were probably more thoroughly scrutinized for this pathogenic action, it is impossible to say. However, it seems evident that lesions are frequently not found because, in many instances, the period between infection and autopsy has been too long.

Applying the criterium of direct animal transmissibility, my strains belong, with the possible exceptions noted, to the saprophytic group. Nevertheless, it is worthy of note that all my strains, with the exception of one (B) were derived from patients who had tuberculosis or such undiagnosed lesions that are suggestive of tuberculosis. It is probably not wise at the present stage of our knowledge to exclude summarily the possibility that some of these strains may have had some pathogenic significance. On the other hand, it should be emphasized that the finding of such bacilli does not in the least justify the diagnosis of tuberculosis.

The lesions produced by these chromogenic strains are probably not specific for these particular strains but represent the typical response to acid-fast organisms of low virulence in which the foreign-body reaction dominates over the destructive and toxic effects. The resemblance to true tuberculosis was probably overemphasized in some studies (Lubarsch (14), Mayer (15), Sato and Brauer (27), Jaffé (9)). I agree fully with Hoelscher (8) that obvious differences are suppuration instead of caseation, and the scarcity of proliferative processes. In addition, the polymorphism of the inflammatory tissue should be pointed out.

Control series of animal experiments were performed with *B. phlei*

and with a chromogenic acid-fast bacillus from tap-water. Both these strains grew much more rapidly than the strains from human material; their colonies were rough and dry. In large doses (10 mgm. or more) they produced on subcutaneous injection, local abscesses that healed promptly, usually without fistula-formation. These two strains never produced lesions in lymph nodes or in organic parenchymal tissue. This may be interpreted as an essential, and not only a quantitative difference.

In regard to the two instances of apparent increase in virulence (strains D and Cr), extreme caution in interpretation is indicated, particularly since these findings could not be reproduced in a large number of subsequent attempts. However, it seemed justified to report these observations because reasons were cited that might indicate that these findings are probably not caused by simple contamination.

In phylogenetic speculations about the acid-fast group of bacilli one arrives unavoidably at the logical postulate that the mammalian tubercle bacilli are derived from the saprophytic bacilli of the soil and plants. But the actual observational or experimental proof of such a transformation is totally lacking.

SUMMARY

Fifteen strains of chromogenic acid-fast bacilli were isolated from various human material. Their general bacteriological characteristics are described. In animals they produce benign and self-healing lesions that are definitely distinguishable from tuberculosis. These organisms are not transferable in series through animals, and on the basis of this criterium they are grouped as saprophytic acid-fast bacilli. The significance of their presence in human tissues or secretions is still *sub judice*. Their occurrence is frequent enough to constitute a warning in diagnostic procedures.

Two of the fifteen strains underwent an apparent increase in virulence; but since this finding could not be reproduced its interpretation is open to doubt.

REFERENCES

(1) Brem, W. V.: Jour. Am. Med. Assoc., 1909, liii, 909.
(2) Clegg: Philippine J. Sc., 1909, iv, 77, 403.
(3) Crouzon, O., and Villaret, M.: Rev. tuberc., 1903, x, 188.
(4) Cummins, S. L., and Williams, E. M.: Tubercle, 1933, xv, 49.
(5) Daines, L. L., and Austin, H.: Jour. Am. Vet. Med. Assoc., 1932, lxxx, 414.
(6) Daines, L. L., and Austin, H.: Amer. Rev. Tuberc., 1933, xxvii, 600.

(7) GRIFFITH, A. S.: Tubercle, 1933, xv, 53.
(8) HOELSCHER: München. med. Wchnschr., 1901, xlviii, 1483.
(9) JAFFÉ, R.: Deutsche med. Wchnschr., 1921, xlvii, 734.
(10) KARLINSKI, J.: Centralbl. f. Bakt., Abt. i, 1901, xxix, 521.
(11) KIRCHNER, O.: Ibid., (Orig.), 1932, cxxiv, 403; Ztschr. f. Immunitätsforsch. u. exper. Therap., 1932, lxxiv, 56; Beitr. Klin. Tuberk., 1932, lxxx, 460.
(12) KORN: Centralbl. f. Bakt., 1900, xxvii, 481.
(13) KRAUSE, A. K.: J. Outdoor Life, 1920, xvii, 222, 260, 279.
(14) LUBARSCH, O.: Ztschr. f. Hyg. u. Infektionskr., 1899, xxxi, 187; Virchow's Arch., 1913, ccxiii, 417.
(15) MAYER, G.: Virchow's Arch., 1900, cxl, 324.
(16) MERTEN, R.: Zentralbl. f. Bakt., Orig., 1933, cxxviii, 488.
(17) MIRONESCU, T.: Ztschr. f. Hyg., 1901, xxxviii, 497.
(18) MOELLER, A.: Deutsche. med. Wchnschr., 1898, xxiv, 376.
(19) PETRI: Arb. anat. Inst. Kaiserlich-Japan. Univ. zu Sendai., 1898, xiv, 1.
(20) PINNER, M.: Proc. Soc. Exper. Biol. & Med., 1932, xxx, 214; J. Bact., 1933, xxv, 576.
(21) POPPER, H., BODART, F., AND SCHINDLER, W.: Virchows Arch., 1932, cclxxxv, 789.
(22) POPPER, H., BODART, F., AND SCHINDLER, W.: Ibid., 1932, cclxxxvi, 615.
(23) POTET: Thèse de Lyon, 1902.
(24) RABINOWITSCH-KEMPNER, L.: Ztschr. f. Hyg. u. Infektionskr., 1897, xxvi, 90.
(25) RABINOWITSCH-KEMPNER, L.: Deutsche med. Wchnschr., 1900, xxvi, 257.
(26) RABINOWITSCH-KEMPNER, L.: Med. Welt, 1931, v, 1669.
(27) SATO, J., AND BRAUER, A.: Ztschr. f. Fleisch u. Milchhyg., 1901, xii, 11.
(28) SCHWABACHER, H.: Med. Res. Council, Spec. Rep. Ser., 1933, no. 182.
(29) THOMSON, H. M.: Amer. Rev. Tuberc., 1932, xxvi, 162.
(30) TIEDEMANN, H. J.: Zentralbl. f. Bakt., Orig., 1932, cxxii, 483.

ATYPICAL ACID-FAST MICROÖRGANISMS

IV. Smooth-Growing Tubercle Bacilli

MAX PINNER[1]

The terms "smooth" and "rough" have been used in connection with tubercle-bacillus colonies isolated by Petroff, Reed and Rice, Seiffert and other authors. Following the example of Petroff, colonies were called "smooth" for certain general bacteriological reasons, but, morphologically speaking, these colonies are not "smooth" at all. This usage has created considerable difficulty and confusion. In this report, the term "smooth" will be applied to colony-formation in its strict morphological sense only. Consequently the "smooth" colonies to be discussed here, have apparently no relation to the "smooth" colonies described by the authors named above.

From the literature it is doubtful whether the type of organisms discussed here has been described before. This report is based on the study of four different strains.

DERIVATION OF STRAINS

1: Strain L: A man, 42 years old, had chronic fibrotic pulmonary tuberculosis with multiple small cavities. This disease was known to have existed for at least 15 years, and it was remarkable because of the frequency of haemoptyses and the slightness of constitutional symptoms. Frequent acute exacerbations would terminate in complete symptomatic recovery after short periods of rest. At present the pulmonary process is quiescent, but tubercle bacilli were demonstrated in the sputum by animal inoculation. For the last nine years the patient had probable tuberculous involvement of the right hip-joint; this has been essentially an ankylosing nondestructive process. Seven years ago a tuberculous left epididymis and testis were removed, and 5 years ago the right epididymis. At this time, renal tuberculosis was suspected, but not definitely confirmed, although acid-fast rods were found in the patient's urine. At the present time, the patient is in excellent physical condition. Uro-

[1] From the Laboratory of the Desert Sanatorium and Institute of Research, Tucson, Arizona.

[2] Presented in part before the Pathological Section of the thirty-first annual meeting of the National Tuberculosis Association, Saranac Lake, New York, June 25, 1935.

logical examination reveals tuberculous involvement of both seminal vesicles and probably of the prostate. The patient has no local symptoms, and a cystoscopic examination was not done. Repeated cultures from the urine yielded white smooth glistening colonies of acid-fast bacilli and, at times, a few colonies of typical tubercle bacilli (human type).

2: Strain H37X: In December, 1931, our incubator became overheated to an unknown degree and for an undetermined time, but for less than 16 hours. Efforts were made to obtain transplants from the cultures which were in the incubator at that time. Some of the attempts were successful, others were not. The transplants from an old stock culture of H37 developed within 5 days, showing smooth glistening creamy white colonies; these colonies were named H37X. Since then, many attempts were made to reproduce this incidental occurrence; cultures of H37 were subjected to various degrees of temperature for various periods; but all these attempts remained unsuccessful.

3: Strain Zi S: From the sputum of a man, suffering from pulmonary tuberculosis and pulmonary coccidioides, tubercle bacilli were isolated. According to their pathogenic action in guinea pigs, rabbits and chickens, and according to their morphology, they were typical human tubercle bacilli. On the third transplant, there appeared, in addition to the typical bread-crumb colonies, white smooth glistening colonies that were easily subcultured in pure culture. The same type of colonies were again isolated from the original strain from a later transplant.

4: Strain Cpt.: A farmer, 50 years old, with a chronic fibrotic apical tuberculosis, had cough and slight constitutional symptoms for the last six years. When in the Sanatorium he expectorated about 2 drams of mucopurulent sputum in 24 hours; on repeated examinations, tubercle bacilli could not be demonstrated. One sputum specimen was injected into a guinea pig which did not develop tuberculosis, but from the same specimen, small round smooth white colonies of acid-fast bacilli were isolated which made their appearance about three weeks after seeding.

GENERAL BACTERIOLOGICAL CHARACTERISTICS

1: Individual morphology: These four strains are acid-fast, gram-positive, nonmotile, non-spore-bearing small rods which are not always definitely distinguishable from true tubercle bacilli. Most of the rods are not more than 3–4 micra in length, and in most smears, particularly from strains L and Cpt there are many minute acid-fast and non-acid-

fast granules.[3] After 24 hours' decolorization in acid-alcohol most of the carbol-fuchsin disappears.

2: Growth: All four strains grow readily on glycerol, egg and potato media. Strain L grows particularly well on glucose-agar. On plain agar there is some scant growth. In liquid glycerol media there is clouding and pellicle-formation. Strain L develops visible colonies within 18 hours. The other three strains require 3 to 5 days for colony development. At room temperature growth does not occur.

3: Appearance of colonies: Fully developed colonies are round in outline, more or less hemispherical, pure white to cream-colored, perfectly smooth, and glistening. Their consistence is that of cream cheese, and sometimes viscous. They are easily suspended in water or saline solution.

Legend to Figs. 1, 2, 3 & 4

(Diagrams showing increase in virulence of "smooth" strains)

Explanation of symbols:

□ = guinea-pig
AT = atypical tuberculosis
Loc = local lesion only
TT = typical inoculation tuberculosis
N = no lesions attributable to infection
Ⓢ = smooth colonies isolated
Ⓡ = typical tubercle bacilli isolated
Kx = killed x days after infection
Dx = died x days after infection
Arrow pointing from square to square = direct animal transfer
Arrow pointing from circle to square = injection of culture
Arrow pointing from circle to circle = test-tube transfer

4: Pathogenicity: In regard to their pathogenic action the microorganisms behave very much the same as the group of chromogenic acid-fast bacilli reported in the preceding paper (1), so that a separate discussion appears superfluous. Infected animals react to tuberculin and to culture filtrates of the homologous strain.

RELATION TO TUBERCLE BACILLI

It appears highly probable that these four strains are smooth and relatively avirulent variants of human tubercle bacilli. This opinion is based on the following evidence:

[3] It may be mentioned parenthetically that, on account of the numerous granules in these strains, large numbers of filtration experiments were done; but no filterable forms could be demonstrated, whether by various culture methods or by animal inoculation.

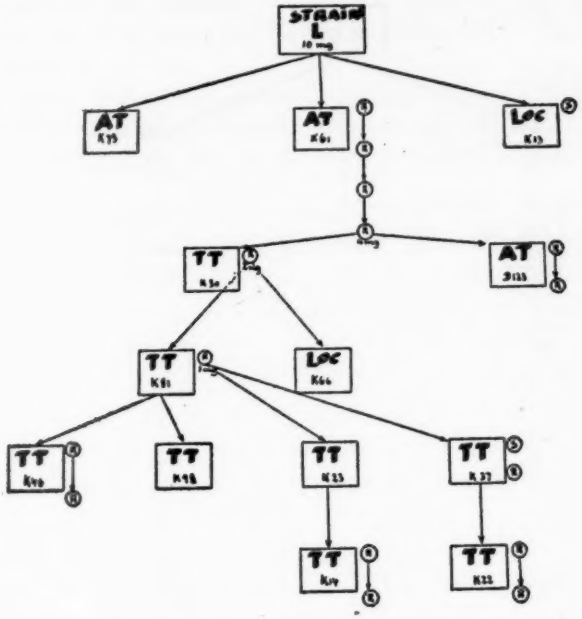

STRAIN L
AT
AT
LOC
TT
AT
TT
LOC
TT
TT
TT
TT
TT
TT

FIG. 1

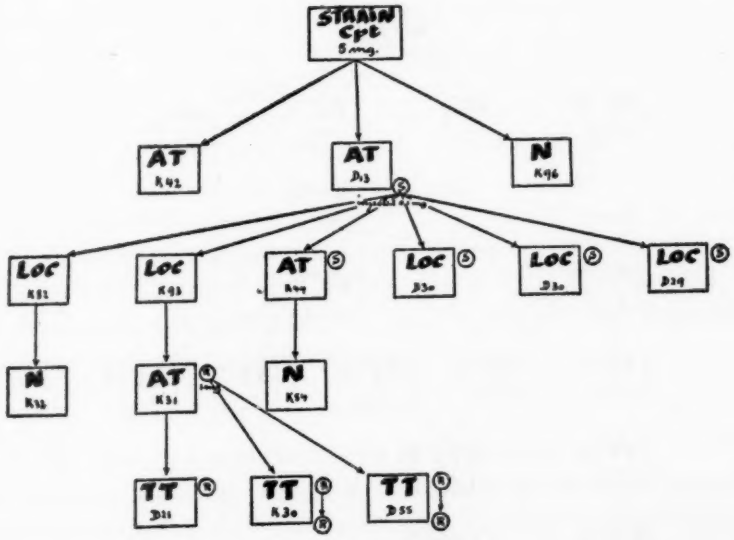

STRAIN Cpt 5 mg.
AT
AT
N
LOC
LOC
AT
LOC
LOC
LOC
N
AT
N
TT
TT
TT

FIG. 2

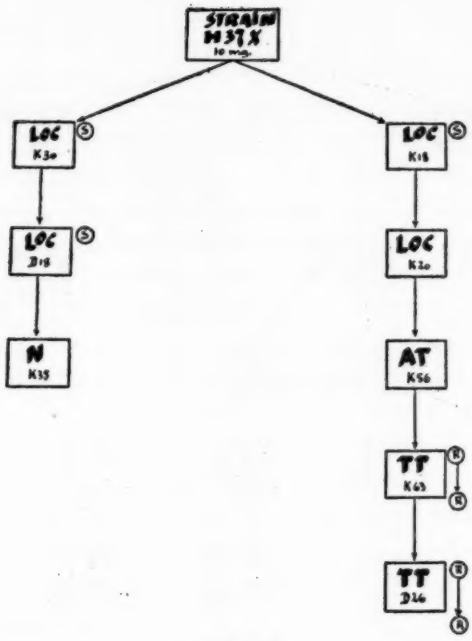

STRAIN M37 X
LOC K30
LOC K18
LOC D18
LOC K20
N K35
AT K56
TT K43
TT D46

FIG. 3

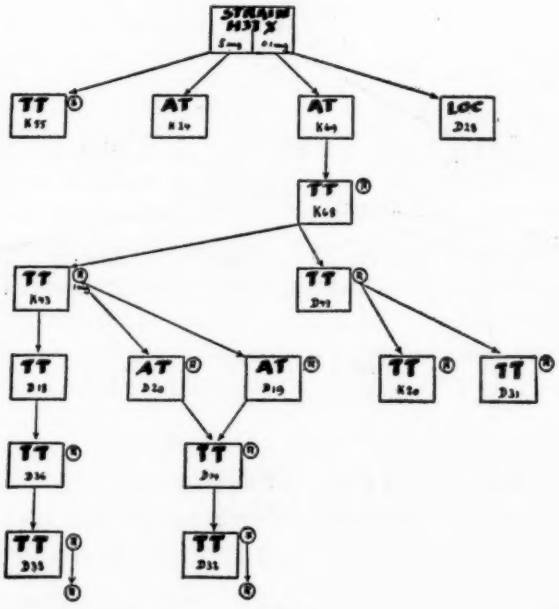

STRAIN M37 X
TT K55
AT K19
AT K49
LOC D28
TT K48
TT K43
TT D27
TT D18
AT D20
AT D19
TT K20
TT D31
TT D36
TT D29
TT D33
TT D32

FIG. 4

1: Three strains (L, Cpt and ZiS), were isolated from excreta from proved tuberculous foci, and strain H37X was derived from a known culture of tubercle bacilli.

2: With three strains (L, Cpt and H37X) it was possible to achieve a transformation into typical human tubercle bacilli. This succeeded once with strains Cpt and L, and twice with strain H37X.

Figures 1 to 4 represent schematically how these transformations were achieved through serial animal transfers. The resulting rough-growing colonies behave entirely like true human tubercle bacilli; their characteristics remained stable in many generations of subcultures.

DISCUSSION

In the preceding paper (1), apparent transmutations of chromogenic acid-fast bacilli into tubercle bacilli were reported. In this connection the possible sources of error were pointed out and the need for caution in interpretation was emphasized. All that was said there applies fully to the present report.

However, it should be remembered that smooth and rough variants have been demonstrated to exist in so many bacterial species, that this duplicity of colony form is quite suggestive of a general bacteriological principle, so that it may not be surprising to find the condition to exist in tubercle bacilli. On the other hand, there is a wealth of evidence that points toward a striking and rigid stability of tubercle bacillus strains in regard to morphology and virulence. Such evidence cannot be dismissed easily, although it has been assailed from many angles during the last decade. The evidence for and against the absolute stability of the biological characteristics of tubercle bacilli stands sorely in need of a critical analysis; it is certainly far from being a settled affair.

The findings reported here present but a small contribution to the general problem mentioned above. Their interpretation is tentative and must remain subject to further studies.

SUMMARY

1. Four strains of acid-fast bacilli are described.

2. They are distinctly different from tubercle bacilli in colony and individual morphology, in metabolic requirements and in pathogenicity.

3. Reasons are cited that suggest that these microörganisms are "smooth" variants of human tubercle bacilli.

REFERENCE

(1) PINNER, M.: Amer. Rev. Tuberc., 1935, xxxii, 424.

THE SPORE-BEARING ANAEROBIC BACTERIAL FLORA OF TUBERCULOUS CAVITIES[1]

FRANCIS C. FARAGÓ

The presence of spore-bearing anaerobic bacteria in tuberculous lung cavities claims our attention for several reasons. In the first place, the question is whether anaerobic bacteria can live and multiply under the conditions existing in the cavities; that is to say: Do the pathological changes provoked by the tubercle bacilli produce such conditions as enable the growth of anaerobes? Next, we have to determine what kind of anaerobic organisms are prevalent in the cavities.

The present investigation was concerned with tuberculous cavities. Bronchiectasis, and other types of lung cavities were not available in a sufficient number of cases. Owing to the kindness of Dr. Ödön Zalka, to whom the author wishes to express his appreciation, cadavers from the Saint Stephen Hospital in Budapest could be used for this study. The autopsies were performed within a few hours after death.

The material for examination was obtained in the following way: The chest was opened, and the cavity located and opened under aseptic precautions; fluid from the cavity was withdrawn and a portion of the wall of the cavity was excised. The materials thus obtained were used for cultivation of the anaerobic bacilli according to Zeissler's (1) (2) method. A part of the cavity-wall and the fluid were kept at 80°C. for one hour in order to eliminate vegetative forms of microörganisms. Materials thus treated were transferred in Hibler's brain-broth (3), which is particularly suitable for the multiplication of spore-bearing forms. The mixed cultures obtained after an incubation of 24 to 72 hours in brain-broth were subcultured on plates containing 10 to 20 per cent blood and 2 per cent glucose. On this medium the different kinds of anaerobes were isolated by successive subcultures. Isolated strains grown in brain-broth or in cooked meat-broth were stored in cold room.

For the classification of anaerobic bacteria thus isolated the following means of identification were used.

[1] From the Institute of Bacteriology, Peter Pázmány University, Budapest, Hungary.

1: Macroscopic appearances were studied on blood-agar plates having the same composition in every case. On these plates the anaerobic forms produced characteristic colony-formations.
2: Microscopic characteristics of the various anaerobes were studied by preparations of isolated colonies. The arrangement of bacilli, the position and shape of the spores, the presence or absence of motility, and the capsule-formation were all taken into consideration.
3: Changes produced by the growth's products of anaerobic organisms in some of the media (brain-broth, cooked meat-broth, milk, gelatine) and the fermentation of carbohydrates (glucose, maltose, lactose, glycerine, inulin) were studied and used for identification.
4: The various degrees of heat resistance of spores, which is one of the characteristic properties of anaerobes, were also examined.
5: From the point of view of identification and pathogenicity animal inoculations, described by Weinberg and Seguin (4) and later by Zeissler, are of great importance. In the present study guinea pigs were inoculated intramuscularly with 0.05 cc. of brain-broth cultures, diluted with saline solution to 1 cc. The rapidity of death and the findings at autopsy gave definite information for the identification of the strains.

The details of Zeissler's methods are not mentioned here: these can be obtained by referring to the bibliography of this report, and they are also briefly described in another paper on this subject.

The pulmonary cavities of 30 men of different ages were examined whose deaths were due to tuberculosis. The findings are given in table 1.

From the data shown in the table, it is seen that all the cavities contained anaerobic bacilli. The fluid and the wall of cavities gave the same kind of organisms. In addition to the various pathogenic and non-pathogenic anaerobes, *B. Welchii* was present in every case. Twelve strains of these were strongly pathogenic and two were only slightly so. The inoculation of *B. Welchii* strains in some cases produced the death of the guinea pigs within twenty-four hours with marked toxic symptoms. The other kind of anaerobic bacilli did not show extreme virulence. Some of the *B. Novy* and *Vibrion septique* strains produced death within two to three days.

The data, as summarized in the table, might indicate that the anaerobic bacterial flora of the lung cavities was practically the same as that which occurs in the intestinal tract. Since the material of this investigation was secured almost immediately after death of the patient, there was only a slight chance for these anaerobic bacteria to become generally

disseminated throughout the body. It therefore seemed advisable to determine whether or not these anaerobes existed in the lung cavity

TABLE 1

NUMBER	NAME	AGE	ANAEROBIC BACTERIA ISOLATED	RESULTS OF ANIMAL INOCULATION
1	L. A.	36	B. Welchii	death within 2 days
2	S. T.	28	B. Welchii; B. multifermentans	death within 3 days
3	N. P.	26	B. Welchii; B. sporogenes Metchnikoff	—
4	F. T.	39	B. Welchii	no symptoms after 3–4 days
5	S. T.	57	B. Welchii; B. oedematis maligni	death within 1 day
6	F. K.	32	(a) B. Welchii; (b) B. Welchii	death within 2 days
7	G. F.	21	B. Welchii	—
8	S. L.	33	B. Welchii; B. tetanomorphus	—
9	B. M.	18	B. Welchii; B. putrificus tenuis	death within 1 day
10	K. F.	51	B. Welchii	—
11	F. A.	39	B. Welchii	—
12	L. T.	30	B. Welchii	death within 2 days
13	E. T.	24	B. Welchii	death within 1 day
14	S. B.	36	B. Welchii; B. amylobacter	—
15	B. T.	27	B. Welchii; B. Novy; B. sporogenes Metchnikoff	death within 3 days
16	B. F.	29	B. Welchii; B. oedematis maligni	death within 2 days
17	Z. G.	35	B. Welchii	—
18	H. G.	32	B. Welchii	—
19	K. F.	25	B. Welchii; B. putrificus tenuis	no symptoms after 4 days
20	B. A.	30	B. Welchii	death within 2 days
			B. Novy	death within 3 days
21	S. T.	22	B. Welchii; B. amylobacter	death within 2 days
22	L. G.	28	B. Welchii	—
23	P. L.	29	B. Welchii; B. cochlearius	death within 3 days
24	B. T.	41	B. Welchii; B. Novy	death within 3 days
25	S. T.	30	B. Welchii	—
26	B. J.	33	B. Welchii; B. sporogenes Metchnikoff	—
27	S. E.	34	B. Welchii; B. putrificus tenuis	death within 2 days
28	B. E.	38	B. Welchii	—
29	B. A.	33	B. Welchii	death within 3 days
30	K. K.	21	B. Welchii; B. amylobacter	—

Underlined organisms produced pathogenic conditions.

during the life of the patient. For this purpose sputa from 30 tuberculous patients were submitted for investigation and anaerobic cultures were made. The patients were treated in the Saint Stephen Hospital

in Budapest, but they were not selected by roentgen examination regarding cavities. Positive results were obtained in 10 per cent; three *B. Welchii* strains were obtained, one of which proved to be pathogenic and the two other nonpathogenic.

The result of examination of tuberculous sputum seems to exclude the supposition that the presence of anaerobes in the cavities at autopsy was due to general dissemination after death, and opens a new field for further studies on tuberculous patients.

DISCUSSION

In the present study first the different properties of *B. Welchii* strains deserve special mention. Certain variations in virulence were observed. Some strains killed guinea pigs within twenty-four hours, others caused pathological conditions which gradually diminished, and still others were entirely nonpathogenic. The seriousness and rapidity of the pathogenic progress in guinea pigs inoculated with *B. Welchii* were accompanied by a corresponding amount of haemorrhagic oedema over the area of inoculation and later spreading on the abdominal wall. Similarly, there seemed to exist some correlation between the degree of virulence and the grade of haemolysis observed on the blood-agar plates. On the surface cultures a marked difference in the color and shape of the colonies of the different strains was noticed. The morphology of the stains varied in a certain extent though they were all nonmotile and showed capsules in india-ink preparations. It should be mentioned that in one case two strains, one pathogenic and the other saprophytic, were obtained from the research material. The colonies of these two strains showed a distinct difference on agar plates. Concluding these observations, it might be pointed out that variation of virulence ranging from extreme pathogenicity, causing death in twenty-four hours, to complete absence of virulence was observed.

The finding of a secondary anaerobic invasion in the tuberculous cavities may provoke the following questions:

1: How and from where did the anaerobic bacilli get into the living system?
2: Can *B. Welchii* (or other anaerobes) be present without producing typical and apparently acute lesions?
3: What kind of physiological or pathological responses result from the findings described?

Rassfeld (5), studying the heart-blood of corpses, has found anaerobic bacteria in all cases of ulceronecrotic disease. Regarding the origin of

these anaerobes it was explained by him and admitted also by Zeissler (1928) that the defect of the mucosa, either in the lung or elsewhere, acts as a portal for the secondary anaerobic contamination; and that through this portal *B. Welchii*, among other bacteria, get into the blood-stream. During life, however, they produce no pathological change. On the other hand, very careful investigations were carried out by Branham (6) and by Levinthal (7) to discover the anaerobic flora of the mouth, nose and pharynx. Although various kinds of anaerobic cocci and spirochaetes were found in these experiments, anaerobic bacilli were not met with. The correctness of Rassfeld and Zeissler's explanation is not necessarily excluded by the findings of Branham and Levinthal, but, after all, the question of the portal of secondary invasion seems to remain open.

Is there any chance of the presence of *B. Welchii* without producing acute gas gangrene? This point has been answered by Cornell's (8) (9) investigation. Cornell produced an artificial chronic infection with *B. Welchii* in rabbits, carrying out experiments regarding the aetiology of anaemia. The infected rabbits, having pathological changes in the blood cells, died in convulsions after a chronic diarrhoea, but never developed acute gas gangrene. These experiments might prove that *B. Welchii* infection can exist without causing typical gas gangrene.

It remains an open question whether the pathogenic anaerobic organisms, which are present in the cavities as secondary invaders, play an active rôle in the pathological process. It may be possible that the presence of virulent, toxogenic organisms are also of significance.

SUMMARY

Positive cultures of *B. Welchii* were obtained from 100 per cent of tuberculous cavities bacteriologically studied within a few hours of death. Other species of pathogenic and nonpathogenic anaerobes were isolated from a smaller percentage of cases. Forty-two per cent of the *B. Welchii* strains cultivated from cavities proved to be pathogenic.

Sputa from tuberculous patients also gave positive results in 10 per cent of the cases.

The present study was made under the direction of Prof. Stephen Went. The author expresses his most sincere appreciation and thanks for his guidance.

REFERENCES

(1) ZEISSLER, J.: Handbuch der pathog. Mikroorg., 1928, iv, 1097.
(2) ZEISSLER, J.: Ibid., 1930, x, 35.
(3) HIBLER, A.: Untersuch. über die pathog. Anaeroben, 1908, Teba.
(4) WEINBERG, M., AND SEGUIN, P.: La gangrene gaseuse, 1918, Paris.
(5) RASSFELD, L.: Ztschr. Hyg., 1921, xciii, 393.
(6) BRANHAM, S.: J. Inf. Dis., 1927, xli, 203.
(7) LEVINTHAL, W.: Zentralbl. Bakt., Orig., 1928, cvi 195.
(8) CORNELL, B.: J. Inf. Dis., 1925, xxxvi, 425.
(9) CORNELL, B.: Ibid., 1925, xxxvi, 508.

THE PRESENCE OF B. WELCHII IN TUBERCULOUS CAVITIES[1]

FRANCIS C. FARAGÓ

In a previous study (1) the anaerobic organisms present in tuberculous cavities at autopsy were investigated. *B. Welchii* was found in 100 per cent of the cases, and 42 per cent of the isolated strains were pathogenic. Since it might be argued that these organisms reached the tuberculous cavities after death, attention was directed in the present study to sputa from cavity cases during life, and, as a further control, lung tissue from cases dying of other diseases was obtained a few hours after death and cultured anaerobically. With regard to this control autopsy material, in only one case out of eight were any anaerobic organisms found.

Examination of Sputum

The sputa were obtained from Middlesex County Sanatorium patients showing definite cavities by X-ray examination. Zeissler's (2) method for detecting anaerobic organisms was used, and the technique is briefly as follows:

A part of the sputum was put in brain-broth medium (Hibler (3)), in order to provide suitable anaerobic conditions. After 48 hours' incubation in the brain-broth, the culture was examined for the presence of gram-positive bacilli and, if positive, was plated out on one side of an agar plate containing 10 per cent blood and 2 per cent glucose. On the other side of the plate, *B. prodigiosus* was heavily inoculated. To prevent any possible contamination of the brain-broth culture by *B. prodigiosus*, a narrow strip of the blood-agar can be cut out sterilely across the centre of the plate before the plate is inoculated, thus placing a gap between the two cultures. The inoculated plate is then hermetically sealed to a glass plate with plasticine and incubated for 48 to 72 hours. Isolation of pure strains are carried out in the same way.

Thirty-four sputa from cavity cases were examined in this way, and from four of them (12 per cent) *B. Welchii* was isolated. The organisms were identified as B. Welchii on the following criteria:

[1] From the Department of Bacteriology and Immunology, Harvard University Medical School, Boston, Massachusetts.

Blood-agar plates: Round colonies with raised centre surrounded by haemolytic zone, if grown under anaerobic conditions. No growth aerobically.
Brain-broth: Abundant gas production; no blackening of medium.
Morphological appearance: Organisms from surface colonies after 48 hours' incubation were gram-positive bacilli of varying length with no tendency to spore formation. Nonmotile. Old cultures showed involution forms.
Fermentation: Stormy clot in litmus milk. Gas-formation in glucose, maltose, lactose, glycerine, and inulin. Acid-formation in maltose, not in glucose or lactose. Two strains formed acid in glycerine, two in inulin.

Serological Examinations

As a corollary to finding *B. Welchii* in tuberculous cavities at autopsy and in sputum during life, it was thought that it might be possible to demonstrate antibodies in the serum, if *B. Welchii* were antigenic under these conditions. Unfortunately, there is little known about agglutinins, precipitins, etc., against *B. Welchii*, and what evidence there is points to a great diversity of strains, so that this avenue of approach held out little hope. The haemolysin, however, and the exotoxin are common to all the different strains. Accordingly, an attempt was made to detect the presence of antihaemotoxin and antitoxin in the sera of cavity cases. *Antihaemotoxin:* Henry's (4) *in vitro* method was used to demonstrate the presence of antihaemotoxin in the serum.

Technique

The haemolytic unit is arbitrarily fixed by Henry as "the smallest amount of haemotoxin which will produce 20 per cent haemolysis in 1.0 cc. of a 6 per cent rabbit corpuscle suspension, the mixture of haemotoxin and corpuscles being made up to a volume of 2.5 cc. and incubated at 37°C. for 2 hours." The corpuscles are washed three times before their suspension in saline solution, and the same rabbit should be used throughout, as the cells of different rabbits vary in susceptibility. Since fluid haemotoxin deteriorates by oxidation, dried haemotoxin was prepared by Henry and Lacey's (5) method. The culture filtrate was precipitated by ammonium sulphate, the precipitate dissolved in distilled water, reprecipitated in absolute alcohol, and dried *in vacuo*. The powder thus obtained was dissolved in the proportion of 0.01 gm. in 10.0 cc. of salt solution, and 0.10 cc. of this solution contained one Henry's haemolytic unit. The inhibiting action of the various sera on this haemotoxin solution was then tested in the following way: 0.5, 0.35, and

0.2 cc. of the haemotoxin solution was placed into three tubes, each containing 0.5 cc. of the patient's serum, previously inactivated at 56°C. for one hour. The volume in each tube was made up to 1.5 cc. with saline solution, and the tubes incubated for thirty minutes. One cubic centimetre of the corpuscular suspension was added to each of the tubes, which were then incubated at 37°C. for 2½ hours, each tube being

TABLE 1

POSITIVE CAVITY CASES					CONTROL CASES*				
Number	Patient	Haemolysis in per cent			Number	Patient	Haemolysis in per cent		
		0.5 cc. toxin dilution	0.35 cc. toxin dilution	0.20 cc. toxin dilution			0.5 cc. toxin dilution	0.35 cc. toxin dilution	0.20 cc. toxin dilution
1	P. K.	40	20	—	1	V. C.	70	50	30
2	K. C.	70	50	30	2	I. C.	70	50	30
3	Mc. K. G.	70	50	30	3	Z. L.	60	40	20
4	S. J.	40	20	—	4	Mc. D.	70	50	30
5	G. F.	70	50	30	5	W. M.	65	40	25
6	P. M.	70	50	30	6	S. R.	70	50	30
7	N. H.	30	10	—	7	K. F.	70	50	30
8	D. M.	70	50	30	8	A. B.	70	50	30
9	B. J.	70	50	30	9	W. S.	70	45	30
10	Mc. G. F.	70	50	30	10	M. L.	70	50	30
11	L. C.	20	—	—	11	S. F.	70	50	30
12	C. B.	20	—	—	12	G. J.	65	50	25
13	O'K. J.	70	50	30	13	I	70	50	30
14	B. L.	40	20	—	14	II	65	45	25
15	K. F.	65	40	25	15	III	60	40	20
16	Mc. L. M.	40	20	—	16	IV	70	50	30
17	Mc. F. B.	70	50	30	17	V	70	50	30
18	M. L.	40	30	—					
19	Mc. C.	20	—	—	No serum		70	50	30
20	S. A.	70	50	30					
21	O. I.	70	50	30					

* Nos. 1–6: patients, noncavity cases or cavity questioned.
Nos. 7–12: patients having various febrile diseases.
Nos. 13–17: Sera Wassermann positive or negative.

shaken every 20 minutes. The tubes were then read by comparing the degree of haemolysis with a haemoglobin scale. This scale was made by completely laking 1.0 cc. of the corpuscular suspension in a volume of 2.5 cc., and then diluting this haemoglobin solution in a series of tubes.

Twenty-one sera from cavity cases, and 17 control sera were tested in this way. The control sera were obtained from tuberculous patients

showing no cavity-formation, and from patients suffering from other diseases. The results are shown in table 1. It will be seen that none of the control sera exerts any definitely inhibiting effect on the action of the haemotoxin, while 9 out of 21 sera (42.8 per cent) from cavity cases show a definite inhibition of the haemotoxin.

TABLE 2

CAVITY CASES						CONTROL CASES*					
Number	Patient	Toxin		Heated toxin (Control)		Number	Patient	Toxin		Heated toxin (Control)	
		After 8 hours	After 24 hours	After 8 hours	After 24 hours			After 8 hours	After 24 hours	After 8 hours	After 24 hours
1	P. K.	±	±	±	±	1	V. C.	+	+	−	−
2	K. C.	+	+	−	−	2	I. C.	+	+	−	−
3	Mc. K. G.	+	+	−	−	3	Z. L.	±	±	−	−
4	S. J.	−	−	−	−	4	Mc. D. M.	+	+	−	−
5	G. F.	+	++	−	−	5	W. M.	+	+	−	−
6	P. M.	+	+	−	−	6	S. R.	++	++	−	−
7	N. H.	−	−	−	−	7	S. F.	+	+	−	−
8	D. M.	+	+	−	−	8	D. M.	+	+	−	−
9	B. T.	+	++	−	−	9	C. P.	+	+	−	−
10	Mc. G. F.	+	+	−	−	10	K. F.	+	+	−	−
11	L. C.	±	±	−	−	11	A. B.	++	++	−	−
12	C. B.	−	−	−	−	12	W. S.	+	+	−	−
13	O'K. J.	+	+	−	−	13	M. L.	+	+	−	−
14	B. L.	+	−	−	−	14	S. F.	+	+	−	−
15	K. F.	+	+	−	−	15	G. J.	+	+	−	−
16	Mc. L. M.	−	−	−	−	16	F. F.	++	+	−	−
17	Mc. F. B.	+	+	−	−	17	G. E.	+	+	−	−
18	M. L.	++	++	++	++	18	P. O.	+	+	−	−
19	B. C.	+	+	−	−	19	H. K.	++	++	−	−
20	H. F.	±	−	−	−	20	T. L.	+	+	−	−
21	S. A.	+	+	−	−						
22	F. C.	−	−	−	−						
23	K. H.	++	+	−	−						

* 1–9: patients, noncavity or cavity questioned.
10–15: patients having various febrile diseases.
16–20: normal.

Antitoxin

In order to test for the presence of *B. Welchii* antitoxin, intracutaneous injections were carried out on patients with cavities, and a number of controls.

The toxin was prepared in the same way as for the haemotoxin from the same pathogenic strain (Lederle P.D. 1). The intracutaneous method of testing for antitoxin has been described by Roemer (6). The test-dose was carefully worked out by the author on himself. Actually, the amount used corresponded to 1.5 Henry's haemotoxin units in this particular preparation. At the same time that the toxin was injected into the skin of one forearm, a similar amount of heated toxin was injected into the skin of the other arm. If the reaction was positive, a red flush appeared about two hours after the injection of the toxin, and the reaction reached its maximum in 20 to 24 hours, being a red and slightly swollen area, 1.0 to 1.5 cm. in diameter. Pseudoreactions are recognized as red, swollen areas on both arms.

Twenty-three patients with cavities were tested in this way, together with 20 control patients who included tuberculous patients either with no cavity formation, or where the presence of a cavity was doubtful. With one or two exceptions the same cavity patients, whose serum had been examined for antihaemotoxin, were tested. The reactions to the injection of the toxin are given in table 2. It will be noted that none of the control patients showed any neutralization of the toxin, while those cavity cases, whose serum inhibited the action of the haemotoxin, showed either a partial or complete neutralization of the toxin.

DISCUSSION

The isolation of *B. Welchii* from a definite though small percentage of sputa from cavity cases of tuberculosis, lends support to the view that their presence in the cavities at autopsy is not due to dissemination of the organisms after death. While there can be little doubt that conditions suitable for the growth of anaerobic organisms exist in these cavities, the path of invasion by anaerobic bacilli is quite problematical. Spirochaetes have been found in bronchiectatic cavities; but these organisms are present in the pharynx, whereas Branham (7) and Levinthal (8) failed to discover any anaerobic bacilli in the mouth, nose or pharynx.

The question of whether these organisms exert any harmful effect on the host is obviously very difficult to answer. The fact that, in a certain number of cavity cases, there was evidence of the formation of antibodies against the haemotoxin and the toxin of *B. Welchii*, would suggest that the products of the organism are absorbed from the cavity; but, whether in sufficient amount to affect the health of the patient or to retard the process of healing, it is impossible to say at present.

CONCLUSIONS

1. *B. Welchii* was isolated from 12 per cent of sputa obtained from cases of tuberculosis with cavity-formation.

2. Antibodies against the haemotoxin and toxin of *B. Welchii* were detected in 42 per cent of cases of tuberculosis with cavity-formation.

The above study was conducted under the direction of Professor Hans Zinsser and the kind advice of Dr. H. K. Ward, to whom the author wishes to express his thanks and appreciation.

REFERENCES

(1) Faragó, F.: Magyar Orvosi Hetilap, 1933, v, 100.
(2) Zeissler, T.: Handb. der pathog. Microorg., 1930, x.
(3) Hibler, A.: Untersuchsingen über die pathog. Anaeroben, 1908, Jena.
(4) Henry, H.: J. Path. & Bact., 1922, xxv, 1.
(5) Henry, H., and Lacey, M.: Ibid., 1919, xxiii, 273.
(6) Roemer, P. H.: Ztschr. Immunitätsforsch. u. exper. Therapie, 1909, iii, 208.
(7) Branham, S.: Jour. Infect. Dis., 1927, xli, 203.
(8) Levinthal, W.: Zentralbl. Bakt., Orig., 1928, i, 106 & 195.

A SEROLOGICAL STUDY EMPHASIZING THE HYDROGEN-ION CONCENTRATION OF THE BLOOD

In Conjunction with the Red-Cell Sedimentation Test, Leucocytic Index and Complement-Fixation Test

K. T. SASANO[1]

The influence of the acid-base equilibrium upon many biological phenomena is now generally recognized. The action of antibodies and ferments depend largely upon the establishment of a proper acidity or alkalinity in the medium. The growth and products of growth of bacteria are greatly influenced by the acid-base equilibrium of the media in which they are cultivated. In some diseases of man, a marked disturbance in the acid-base equilibrium of the blood has been noted. Since a proper maintenance of the acid-base equilibrium is of such fundamental importance we decided to examine the H-ion concentration of the blood in tuberculous cases to determine whether there might be changes of significance in this disease.

The extreme limits, as reported in the literature, of the blood in various diseases are from pH 7.0 to 9.0, while in health the range is from 7.34 to 7.50. Many conditions other than infections or organic diseases are recognized as having some effect upon the H-ion concentration of the blood. A change toward the acid side may be caused by a decrease of alkaline buffers, as in starvation, retention of nonvolatile acids, ingestion of methyl alcohol, etc.; or by an increase of the carbon-dioxide content, as in morphine poisoning, cardiac failure, emphysema or an excessive intake of carbon-dioxide. An increased alkalinity may be found when the alkaline buffers are increased, as in large intake of sodium bicarbonate, pyloric or high intestinal obstruction and decrease in blood calcium; or a decrease of the carbon-dioxide content of the blood as in hyperpnoea, anoxaemia, and prolonged exposure to a high, humid temperature. It is also reported that a change in the cellular and haemoglobin content has an effect upon the pH of the blood.

A true H-ion concentration of the blood is very difficult to obtain,

[1] The Hegeman Memorial Research Laboratory of the Metropolitan Life Insurance Company Sanatorium, Mt. McGregor, New York.

due to its sensitivity to changes following removal from its natural environment. However, a reliable relative pH value may be obtained if a constant technique for such examination is followed.

CHOICE OF METHOD

An electrometrical method, using quinhydrone and platinum electrodes, was tried. It was unsatisfactory because of (1) drifting and (2) difficulty in manipulation of the blood under oil. Finally, the colorimetric method of Hastings and Sendroy (1) was chosen. With this method a difference of pH 0.025–0.0125 could be detected by interchanging the acid and alkaline standard tubes.

EXAMINATION

All the blood samples were venous, and were taken before breakfast at 7:30–8:30 A.M. The comparison of the color was made within one hour. The blood for sedimentation and complement-fixation tests was taken at the same time, while the total and differential leucocytic counts were made as near the same time as possible.

Five hundred and fifty-five patients and 55 employees were examined during this study. One hundred and ninety-five of these were repeatedly tested two to four times. The H-ion concentration of the blood in the normal controls varied from 7.350–7.410, with an average of 7.384; and in 338 nontuberculous patients, on admission, from 7.30 to 7.485, with an average of 7.393. The blood pH of 177 tuberculous patients on admission varied from 7.35–7.475, with an average of 7.398. Forty complete bed-patients, who were not critically ill, had a pH variation of 7.375–7.475 with an average of 7.411. Over 95 per cent of all the bloods examined had a pH within the so-called normal range.

In the following paragraphs, the "acid side" is indicated when the pH is below 7.37, and the "alkaline side" when above 7.39 with 7.37–7.39 considered as the "normal range."

Of 217 tuberculous patients examined, 61 had complete records of other tests on admission and at discharge. Of these, 28 were minimal, 23 moderately advanced and 10 far advanced cases. The average pH of the blood of these patients on admission and on discharge was 7.397 and 7.393, respectively. The minimal group had an average of 7.394 and 7.393; the moderately advanced, 7.398 and 7.391; and the far advanced 7.405 and 7.401. The average pH of all was on the alkaline side, with the discharge pH slightly less alkaline than the admission pH.

TABLE 1 (A)

Normal controls

SEX	BLOOD-GROUP	pH	SEDIMENTATION	WASSERMANN
M	0	7.385	5	Negative
F	AB	7.400	8	Negative
M	0	7.410	4	Negative
M	0	7.350	3	Negative
F	A	7.385	4	Negative
F	B	7.375	4	Negative
M	B	7.400	2	Negative
F	A	7.400	6	Negative
F	A	7.400	7	Negative
F	0	7.375	5	Negative
F	A	7.400	3	Negative
F	0	7.375	7	Negative
M	A	7.375	2	Negative
M	0	7.375	2	Negative
M	0	7.375	3	Negative
M	A	7.395	3	Negative
M	0	7.395	4	Negative
M	0	7.395	3	Negative
M	0	7.400	2	Negative
M	0	7.395	2	Negative
M	A	7.395	3	Negative
M	0	7.395	3	Negative
M	0	7.365	2	Negative
M	0	7.365	2	Negative
M	A	7.375	1	Negative
M	A	7.375	2	Negative
F	A	7.385	5	Negative
M	A	7.365	1	Negative
M	AB	7.385	2	Negative
M	A	7.385	2	Negative
M	0	7.385	1	Negative
M	A	7.385	8	Negative
F	A	7.395	5	Negative
M	0	7.375	2	Negative
M	0	7.385	2	Negative
F	0	7.385	5	Negative
F	A	7.375	5	Negative
M	0	7.375	3	Negative
M	0	7.375	2	Negative
M	A	7.375	2	Negative
M	0	7.395	3	Negative
M	A	7.395	2	Negative
M	0	7.375	2	Negative
F	A	7.395	5	Negative
M	B	7.375	2	Negative

TABLE 1 (A)—*Concluded*

SEX	BLOOD-GROUP	pH	SEDIMENTATION	WASSERMANN
F	A	7.385	2	Negative
M	A	7.395	3	Negative
F	A	7.365	5	Negative
M	AB	7.385	4	Negative
M	0	7.390	2	Negative
F	A	7.390	6	Negative
M	A	7.385	5	Negative
F	0	7.375	3	Negative
F	0	7.365	6	Negative
F	B	7.365	8	Negative

TABLE 1 (B)

Nontuberculous patients

CASE NUMBER	DIAGNOSIS	BLOOD-GROUP		pH		SEDIMENTATION TEST		WASSERMANN		CLINICAL STATUS ON DISCHARGE
		Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	
6,500	Conv. pneumonia	0	0	7.365	7.375	6	3	0	0	Cured
6,204	Art. sclerosis	AB	AB	7.475	7.385	10	2	0	0	Unimproved
6,396	Psychoneurosis	0	0	7.375	7.385	6	2	0	0	Improved
6,454	Br. abortus inf.	A	A	7.400	7.400	2	1	0	0	Improved
6,476	Conv. pneumonia	0	0	7.400	7.375	8	2	0	0	Cured
6,432	Hyperthyroidism	B	B	7.445	7.375	6	3	0	0	Cured by operation
6,372	Chr. bronchitis	A	A	7.365	7.400	2	2	0	0	Improved
6,421	Art. sclerosis	AB	AB	7.450	7.440	2	2	0	0	Unimproved
6,470	Conv. pneumonia	0	0	7.400	7.395	14	3	0	0	Cured
6,453	Duodenal ulcer	0	0	7.385	7.395	4	2	0	0	Improved
6,485	Prostatitis	0	0	7.395	7.395	2	2	0	0	Cured
6,460	Constipation	A	A	7.385	7.365	3	3	0	0	Improved
6,409	Chr. gastritis	A	A	7.375	7.375	7	2	0	0	Cured by operation
6,351	Bronchitis	A	A	7.415	7.400	2	2	0	0	Improved
6,383	Abscess lung	A	A	7.395	7.375	6	3	0	0	Cured
6,314	Fibrosis myocardium	A	A	7.365	7.365	6	2	0	0	Improved
6,436	Serofibrin. pleurisy	B	B	7.395	7.400	6	3	0	0	Improved
6,449	Cervicitis	A	A	7.400	7.395	2	2	0	0	Unimproved
6,414	Duodenal ulcer	A	A	7.375	7.395	2	2	0	0	Improved
6,420	Diabetes mellitus	0	0	7.375	7.375	13	8	0	0	Improved

TABLE 1 (B)—*Continued*

CASE NUMBER	DIAGNOSIS	BLOOD-GROUP		pH		SEDIMENTATION TEST		WASSERMANN		CLINICAL STATUS ON DISCHARGE
		Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	
6,442	Duodenal ulcer	A	A	7.395	7.400	7	3	0	0	Improved
6,184	Syphilis	0	0	7.395	7.395	6	7	++++	++++	Improved
6,186	Disseminated sclerosis	0	0	7.400	7.385	3	3	0	0	Unimproved
6,403	Duodenal ulcer	A	A	7.365	7.375	3	5	0	0	Improved
6,290	Art. sclerosis	B	B	7.415	7.400	21	13	0	0	Unimproved
6,413	Chr. appendicitis	0	0	7.425	7.385	12	14	0	0	Improved
6,337	Duodenal ulcer	0	0	7.385	7.385	3	1	0	0	Improved
6,575	Hypertension ess.	A	A	7.425	7.375	3	7	0	0	Unimproved
6,580	Cystitis	A	A	7.395	7.400	15	10	0	0	Improved
6,588	Chr. arthritis	0	0	7.415	7.315	15	23	0	0	Improved
6,610	Psychoneurosis	0	0	7.425	7.365	6	11	0	0	Improved
6,631	Gast. neurosis	0	0	7.375	7.395	6	2	0	0	Improved
6,392	Syphilis (Hg poisoning)	B	B	7.425	7.400	9	6	++++	++	Improved
6,540	Hyperthyroidism	A	A	7.365	7.365	5	6	0	0	Improved
6,594	Hydropneumothorax	0	0	7.385	7.415	2	4	0	0	Cured
6,697	Diabetes mellitus	A	A	7.425	7.400	2	1	0	0	Improved
6,592	Conv. pneumonia	A	A	7.425	7.425	2	3	0	0	Cured
6,603	Arthritis chr.	A	A	7.395	7.375	3	2	0	0	Unimproved
6,307	Fibrosis myocardium	A	A	7.395	7.375	10	4	0	0	Unimproved
6,384	Myxedema	A	A	7.375	7.395	3	1	0	0	Improved
6,465	Art. sclerosis	A	A	7.375	7.365	2	4	0	0	Unimproved
6,490	Rheumatic fever	0	0	7.375	7.425	8	3	0	0	Improved
6,553	Hypertension	0	0	7.385	7.365	3	5	0	0	Unimproved
6,579	Secondary anaemia	0	0	7.385	7.365	5	12	0	0	Improved
6,585	Chr. appendicitis	B	B	7.385	7.375	3	5	0	0	Improved
6,621	Conv. typhoid fever	0	0	7.385	7.365	51	17	0	0	Improved
6,637	Conv. peritonitis	B	B	7.400	7.365	12	4	0	0	Cured
6,626	Menorrhagia	AB	AB	7.385	7.365	9	2	0	0	Cured
6,629	Conv. pneumonia	A	A	7.375	7.365	3	1	0	0	Cured
6,517	Conv. thyroidectomy	A	A	7.375	7.400	3	7	0	0	Cured
6,660	Bronchitis	B	B	7.400	7.415	9	14	0	0	Unimproved
6,572	Endocarditis	0	0	7.400	7.375	3	4	0	0	Unimproved
6,554	Empyema	0	0	7.400	7.375	2	9	0	0	Cured

TABLE 1 (B)—*Continued*

CASE NUMBER	DIAGNOSIS	BLOOD-GROUP		pH		SEDIMENTATION TEST		WASSERMANN		CLINICAL STATUS ON DISCHARGE
		Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	
6,556	Duodenal ulcer	A	A	7.375	7.350	6	6	0	0	Improved
6,633	Undulant fever	0	0	7.375	7.385	5	4	0	0	Improved
6,303	Pneumonoconiosis	0	0	7.375	7.385	8	2	0	0	Unimproved
6,530	Nephritis	0	0	7.375	7.385	4	2	0	0	Cured
6,559	Conv. appendicectomy	0	0	7.375	7.385	3	3	0	0	Cured
6,565	Cancer abd. lymph nodes	A	A	7.415	7.385	20	44	0	0	Improved
6,542	Syphilis	A	A	7.385	7.365	2	52	++++	++++	Improved
6,557	Adhesion peritonium	A	A	7.425	7.385	2	4	0	0	Unimproved
6,382	Gast. ulcer	B	B	7.425	7.400	3	3	0	0	Cured
6,499	Gast. ulcer	A	A	7.385	7.425	3	3	0	0	Improved
6,513	Fracture femur	0	0	7.385	7.385	2	3	0	0	Cured
6,570	Conv. pneumonia	0	0	7.385	7.350	3	9	0	0	Improved
6,332	Cardiovascular dis.	A	A	7.385	7.400	8	27	0	0	Improved
6,412	Ovarian cyst	A	A	7.300	7.425	65	18	0	0	Cured by operation
6,516	Myocardial dis.	0	0	7.395	7.395	2	2	0	0	Improved
6,319	Syphilis	0	0	7.415	7.415	3	7	++++	++++	Improved
6,528	Osteitis deformans	A	A	7.400	7.425	5	8	0	0	Unimproved
6,564	Chr. appendicitis	0	0	7.415	7.400	3	9	0	0	Unimproved
6,424	Conv. pneumothorax	0	0	7.400	7.365	6	3	0	0	Cured
6,296	Rheumatic fever	A	A	7.375	7.425	10	2	0	0	Cured
6,357	Bronchiectasis	0	0	7.375	7.415	24	3	0	0	Cured
6,494	Conv. inguinal hernia	A	A	7.375	7.385	7	2	0	0	Improved
6,428	Neurosis	AB	AB	7.415	7.385	2	2	0	0	Improved
6,417	Art. sclerosis	0	0	7.400	7.395	4	7	0	0	Unimproved
6,540	Mitral insufficiency	A	A	7.365	7.375	5	4	0	0	Improved
6,447	Fibrosis myocardium	B	B	7.425	7.400	22	12	0	0	Unimproved
6,537	Art. sclerosis	0	0	7.400	7.375	5	15	0	0	Unimproved
6,649	Hypertrophy of heart	0	0	7.385	7.400	3	5	0	0	Unimproved
6,386	Art. sclerosis	A	A	7.400	7.415	2	7	0	0	Unimproved
6,558	Spastic pylorus	0	0	7.425	7.400	2	6	0	0	Improved
6,702	Chr. colitis	0	0	7.375	7.365	3	1	0	0	Improved

TABLE 1 (B)—*Continued*

CASE NUMBER	DIAGNOSIS	BLOOD-GROUP		pH		SEDIMENTATION TEST		WASSERMANN		CLINICAL STATUS ON DISCHARGE
		Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	
6,738	Syphilis; diabetes mel.	A	A	7.395	7.395	32	23	++++	++++	Improved
6,569	Empyema	AB	AB	7.385	7.375	2	4	0	0	Improved
6,624	Fibrosis myocard.	AB	AB	7.400	7.385	8	11	0	0	Improved
6,766	Cholelithiasis	0	0	7.400	7.400	2	2	0	0	Improved
6,701	Bronchiectasis	0	0	7.385	7.400	3	3	0	0	Improved
6,640	Chr. appendicitis	B	B	7.385	7.400	9	7	0	0	Cured by operation
6,716	Conv. pneumonia	A	A	7.400	7.385	15	7	0	0	Improved
6,717	Spontaneous pneumothorax	AB	AB	7.415	7.415	2	2	0	0	Improved
6,694	Serofibrinous pleur.	A	A	7.400	7.400	5	4	0	0	Improved
6,702	Chr. colitis	0	0	7.375	7.415	3	2	0	0	Improved
6,789	Conv. herniorrhaphy	A	A	7.375	7.425	2	2	0	0	Improved
6,825	Chr. vaginitis	A	A	7.400	7.425	3	6	0	0	Improved
6,527	Diabetes insipidus	A	A	7.365	7.375	2	4	0	0	Unimproved
6,832	Nephritis	0	0	7.385	7.375	3	3	0	0	Improved
6,634	Bronchiectasis	A	A	7.365	7.425	10	6	0	0	Improved
6,834	Rheumatic heart dis.	A	A	7.375	7.415	15	6	0	0	Died
6,609	Spinal syphilis	A	A	7.400	7.465	7	22	++++	++++	Unimproved
6,673	Chr. nephritis	A	A	7.395	7.385	9	8	0	0	Improved
6,597	Syphilis	B	B	7.400	7.365	2	3	++++	0	Improved
6,682	Duodenal ulcer	0	0	7.400	7.400	11	18	0	0	Improved
6,593	Fibrosis myocardium	A	A	7.385	7.385	3	8	0	0	Unimproved
6,755	Chr. arthritis	0	0	7.385	7.415	9	20	0	0	Improved
6,795	Unresolved pneumonia	B	B	7.415	7.425	5	3	0	0	Improved
6,803	Acute cystitis	A	A	7.385	7.375	13	11	0	0	Improved
6,844	Subaxillary adenitis	0	0	7.425	7.400	18	7	0	0	Improved
6,610	Psychoneurosis	0	0	7.425	7.415	6	5	0	0	Improved
6,622	Tumor thyroid	A	A	7.435	7.400	7	5	0	0	Cured by operation
6,770	Duodenal ulcer	0	0	7.385	7.325	3	8	0	0	Improved
6,823	Chr. cholecystitis	A	A	7.425	7.385	3	4	0	0	Improved
6,838	Chr. cholecystitis	AB	AB	7.425	7.385	4	6	0	0	Improved
6,386	Art. sclerosis	A	A	7.400	7.435	2	7	0	0	Improved

TABLE 1 (B)—*Concluded*

CASE NUMBER	DIAGNOSIS	BLOOD-GROUP		pH		SEDIMENTATION TEST		WASSERMANN		CLINICAL STATUS ON DISCHARGE
		Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	
6,502	Bronchiectasis	0	0	7.385	7.425	3	7	0	0	Improved
6,758	Duodenal ulcer	A	A	7.425	7.415	4	4	0	0	Improved
6,822	Conv. thyroidectomy	B	B	7.425	7.375	11	8	0	0	Improved
6,827	Duodenal ulcer	A	A	7.375	7.400	4	5	0	0	Improved
6,657	Arthritis	A	A	7.365	7.325	68	23	0	0	Unimproved
6,745	Syphilis	A	A	7.415	7.415	1	2	++++	++++	Unimproved
6,767	Cholelithiasis	0	0	7.375	7.415	3	4	0	0	Unimproved
6,801	Duodenal ulcer	A	A	7.365	7.425	12	12	0	0	Improved
6,866	Cardiac neurosis	A	A	7.385	7.415	2	7	0	0	Improved
6,718	Conv. nephrectomy	0	0	7.375	7.385	18	8	0	0	Improved
6,826	Hypertension	A	A	7.350	7.385	5	4	0	0	Unimproved
6,884	Sinusitis	B	B	7.415	7.385	5	4	0	0	Improved
6,695	Fibrosis myocardium	A	A	7.400	7.400	12	11	0	0	Unimproved
6,721	Coronary sclerosis	0	0	7.385	7.385	26	8	0	0	Unimproved
6,723	Anxiety neurosis	AB	AB	7.385	7.400	2	3	0	0	Improved
6,859	Duodenal ulcer	AB	AB	7.400	7.375	4	5	0	0	Improved
6,896	Conv. pneumonia	0	0	7.425	7.400	47	6	0	0	Improved
6,898	Conv. rheumatic arthritis	A	A	7.450	7.415	2	3	0	0	Improved

TABLE 1 (C)

Complete laboratory data of 61 tuberculous patients

CASE NUMBER	DIAGNOSIS	BLOOD-GROUP		pH		SEDIMENTATION TEST		COMPLEMENT-FIXATION TEST		BLOOD INDEX		CLINICAL STATUS ON DISCHARGE
		Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	
6,534	Min.	0	0	7.385	7.415	8	4	++++	++++	15	26	Arrested
6,175	M.A.	0	0	7.415	7.395	14	3	++	++++	33	12	Apparently arrested
6,144	Min.	0	0	7.365	7.415	2	6	0	0	16	22	Arrested
6,154	Min.	0	0	7.425	7.400	2	15	+++	+++	30	30	Arrested
6,168	Min.	0	0	7.425	7.375	5	4	++	+++	8	23	Quiescent
6,128	M.A.	A	A	7.375	7.385	12	6	0	0	15	27	Apparently arrested

TABLE 1 (C) *Continued*

CASE NUMBER	DIAGNOSIS	BLOOD-GROUP		pH		SEDIMENTATION TEST		COMPLEMENT-FIXATION TEST		BLOOD INDEX		CLINICAL STATUS ON DISCHARGE
		Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	
6,183	M.A.	B	B	7.375	7.385	8	4	0	+++	26	0	Arrested
6,325	Min.	A	A	7.400	7.375	3	6	++	++	21	5	Apparently arrested
6,431	M.A.	B	B	7.415	7.395	5	5	+++	+++	53	38	Apparently arrested
6,433	M.A.	0	0	7.395	7.365	10	7	++++	++++	27	26	Arrested
6,539	F.A.	A	A	7.375	7.375	25	10	++++	++++	26	25	Improved
5,114	F.A.	A	A	7.425	7.375	27	10	+++	++++	39	34	Quiescent
6,472	Min.	0	0	7.400	7.415	2	2	++	++	31	25	Unimproved
6,543	Min.	A	A	7.385	7.375	4	6	0	++++	11	27	Apparently arrested
4,964	Min.	0	0	7.365	7.425	22	8	+++	++++	85	24	Arrested
6,475	Min.	0	0	7.375	7.375	4	9	+++	+++	27	39	Arrested
5,223	F.A.	0	0	7.475	7.375	20	3	++++	++++	32	28	Apparently arrested
5,595	M.A.	A	A	7.435	7.375	40	11	++++	++++	32	29	Apparently arrested
6,509	Min.	A	A	7.404	7.365	3	7	+++	+++	25	27	Apparently arrested
6,524	Min.	A	A	7.385	7.365	3	9	++	++	20	23	Apparently arrested
6,379	F.A.	A	A	7.400	7.375	8	8	0	0	32	32	Unimproved
5,525	Min.	0	0	7.430	7.400	8	5	++	++++	15	23	Apparently arrested
6,200	F.A.	AB	AB	7.425	7.400	3	2	+++	++++	1	0	Apparently arrested
6,471	Min.	A	A	7.400	7.385	6	2	++++	++++	20	27	Quiescent
6,143	M.A.	0	0	7.385	7.425	12	2	++++	++++	28	37	Quiescent
5,406	M.A.	B	B	7.385	7.395	3	3	++++	++++	60	44	Quiescent
6,161	M.A.	0	0	7.425	7.375	3	3	0	++	12	29	Quiescent
6,311	Min.	A	A	7.395	7.375	15	13	+++	++++	58	4	Arrested
6,526	Min.	A	A	7.395	7.375	3	8	++	++	57	47	Arrested
6,547	Min.	0	0	7.415	7.395	2	5	+++	++	4	27	Arrested
6,478	Min.	0	0	7.375	7.400	4	9	++	++++	19	6	Arrested
6,280	M.A.	B	B	7.415	7.400	13	2	0	+++	44	25	Apparently arrested
6,521	Min.	0	0	7.385	7.400	2	5	++	++	45	37	Apparently arrested
6,498	F.A.	0	0	7.375	7.385	11	20	++++	++++	33	22	Unimproved
6,607	Min.	0	0	7.415	7.385	6	10	0	++	25	17	Improved
6,395	Min.	0	0	7.375	7.385	6	8	+++	+++	3	0	Improved

TABLE 1 (C)—*Concluded*

CASE NUMBER	DIAGNOSIS	BLOOD-GROUP		pH		SEDIMENTATION TEST		COMPLEMENT-FIXATION TEST		BLOOD INDEX		CLINICAL STATUS ON DISCHARGE
		Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	
6,456	M.A.	A	A	7.375	7.375	3	2	++	++	40	29	Arrested
6,477	Min.	0	0	7.375	7.435	3	6	++	+++	44	23	Arrested
6,479	M.A.	A	A	7.385	7.425	2	1	0	++	34	22	Apparently arrested
6,489	F.A.	A	A	7.385	7.415	15	4	++++	++++	28	19	Quiescent
6,647	Min.	0	0	7.375	7.375	4	4	++	++	32	40	Arrested
6,443	M.A.	B	B	7.385	7.385	3	3	0	0	53	15	Arrested
6,753	Min.	A	A	7.425	7.415	3	9	0	0	11	3	Arrested
5,223	F.A.	0	0	7.375	7.375	3	4	++++	++++	28	25	Apparently arrested
6,496	Min.	A	A	7.400	7.400	9	9	0	++	46	28	Arrested
6,849	M.A.	0	0	7.385	7.385	10	4	++++	++++	36	37	Arrested
5,861	M.A.	0	0	7.435	7.435	28	4	++++	+++	57	24	Arrested
6,551	M.A.	B	B	7.375	7.385	2	5	++++	++++	13	15	Apparently arrested
6,596	Min.	A	A	7.365	7.400	2	6	0	0	27	27	Arrested
6,753	Min.	A	A	7.415	7.400	3	5	0	0	3	17	Arrested
6,613	M.A.	A	A	7.385	7.400	3	3	++	++++	4	20	Quiescent
6,672	Min.	A	A	7.385	7.385	8	7	++	++	32	17	Arrested
6,284	M.A.	A	A	7.425	7.400	8	3	++++	++++	37	12	Arrested
5,562	M.A.	B	B	7.385	7.385	13	20	++++	+++	33	21	Arrested
6,688	M.A.	A	A	7.400	7.400	6	5	++++	++++	31	18	Quiescent
6,136	F.A.	AB	AB	7.375	7.415	45	52	++++	++++	27	80	Worse
6,166	M.A.	0	0	7.415	7.375	52	35	0	0	58	82	Worse
6,794	M.A.	B	B	7.400	7.385	5	18	+++	++	28	27	Improved
6,193	F.A.	A	A	7.375	7.425	7	4	0	++	33	15	Quiescent
6,574	M.A.	0	0	7.385	7.375	30	30	++	0	16	10	Improved
6,625	Min.	0	0	7.400	7.400	13	2	++	++	61	27	Arrested

TABLE 1 (D)

40 tuberculous bed-patients

CASE NUMBER	DIAGNOSIS	BLOOD-GROUPS	pH	COMPLEMENT FIXATION FOR TUBERCULOSIS	WASSERMANN	SEDIMENTATION TEST	LEUCOCYTIC INDEX
5,585	M.A.	0	7.40	++++	0	24–37	37
5,230	I.	0	7.415	+++	0	15–28	50
5,704	M.A.	0	7.385	++++	0	11–21	22
5,820	I.R.	A	7.375	++++	0	29–41	36
4,964	I.	0	7.435	+++	0	16–30	55
5,861	M.A.	0	7.435	+++	0	28–43	30

TABLE 1 (D) *Concluded*

CASE NUMBER	DIAGNOSIS	BLOOD-GROUPS	pH	COMPLEMENT FIXATION FOR TUBERCULOSIS	WASSERMANN	SEDIMENTATION TEST	LEUCOCYTIC INDEX
5,747	F.A.	A	7.385	0	0	20–38	15
5,567	F.A.	A	7.435	++++	0	25–39	34
5,842	I.	B	7.425	+++	0	3– 6	42
5,533	I.	A	7.40	++++	0	12–19	13
6,087	M.A.	0	7.435	+++	0	39–47	28
5,410	F.A.	A	7.435	++++	0	28–35	35
5,250	F.A.	A	7.415	++++	0	14–22	28
5,158	M.A.	0	7.400	++++	0	11–21	34
5,950	M.A.	A	7.450	++++	0	21–31	31
5,135	F.A.	0	7.435	++++	0	11–20	29
5,406	M.A.	B	7.465	++	0	17–31	56
6,014	F.A.	A	7.465	++	0	29–41	56
5,784	F.A.	A	7.395	+++	0	35–45	51
5,791	F.A.	0	7.395	++++	0	21–29	69
5,622	F.A.	A	7.405	++++	0	12–25	21
5,829	M.A.	0	7.405	++++	0	8–20	73
5,634	F.A.	A	7.425	++++	0	27–40	42
5,130	F.A.	0	7.395	++++	0	2– 3	39
6,124	F.A.	A	7.395	++++	0	37–46	7
6,108	M.A.	A	7.395	++++	0	3– 8	29
6,054	F.A.	A	7.405	++++	0	33–48	26
5,758	F.A.	0	7.395	+++	0	32–47	68
5,990	F.A.	0	7.405	++++	0	32–47	33
6,057	M.A.	AB	7.405	++++	0	20–38	47
4,333	F.A.	0	7.375	++++	0	26–42	27
6,011	F.A.	0	7.395	++++	0	32–46	27
5,864	M.A.	B	7.425	++++	0	5–14	19
5,811	M.A.	A	7.375	++++	0	4–13	27
5,127	F.A.	0	7.395	++++	0	20–36	77
5,636	F.A.	0	7.425	++++	0	14–27	63
5,778	I.	0	7.425	0	0	8–21	35
5,903	F.A.	A	7.425	++++	0	14–30	43
6,136	F.A.	AB	7.375	+++	0	45–55	63
6,161	M.A.	0	7.425	0	0	3– 5	13

Further analysis of these cases give the following data: Twenty-four improved toward the normal pH: of these, 11 were minimal, 8 moderately advanced, and 5 far advanced. Thirteen shifted toward either the acid or the alkaline side: of these, 6 were minimal, 4 moderately advanced and 3 far advanced. Nineteen were stationary: of these, 16 were within the normal range and 3 on the alkaline side: 7 were minimal, 10 moder-

ately advanced and 2 far advanced. Three changed from the acid to the alkaline side. All of these were in the minimal group. Two changed from the alkaline to the acid side. One was in the minimal and the other was in the moderately advanced group. (See table 1.)

These figures indicate that (1) the pH of the blood of tuberculous patients was slightly more alkaline than that of nontuberculous patients and of normal controls; (2) at discharge the pH was slightly less alkaline; and (3) complete bed-rest patients had a greater alkalinity than any other group.

A COMPARISON OF pH OF BLOOD, SEDIMENTATION TEST AND LEUCOCYTIC INDEX

In this study a comparison of three tests was made on the 61 tuberculous cases discussed above. To simplify the comparison, an arbitrary division into favorable, stationary and unfavorable groups was made, for each of the three tests. With regard to the pH of the blood a case was considered favorable if the pH approached or remained within a range of 7.37–7.39; stationary, if the variation was no more than 0.01; and unfavorable if the pH shifted toward either the acid or alkaline side. With regard to the sedimentation test, favorable is indicated by a decrease, unfavorable by an increase of more than 2 mm. in one hour, and stationary when the fluctuation was less than two millimeters.

For the interpretation of the leucocytic reaction we have used the leucocytic index recently devised by Crawford (2) to simplify the interpretation placed upon Medlar's (3) leucocytic-reaction interpretation. This index includes the neutrophile-lymphocyte ratio, together with arbitrary values for abnormal total counts and increased percentages of monocytes. The index number begins at zero as the most favorable and increases progressively to 100 plus. The values given by these authors for the index numbers are as follows: 0–15, favorable; 16–26, slightly favorable to slightly unfavorable; 27–35, unfavorable; 36 plus, very unfavorable. The reader is referred to the original articles for more detailed information. For comparing the leucocytic index with two other tests we have taken a decrease in the index number as favorable and increase in number as unfavorable.

Using the above criteria it was found that all these tests agreed in 31 per cent of the cases, with complete disagreement in 5 per cent, and in no instance did any two tests agree in over 56 per cent or disagree in

over 54 per cent of the cases. Table 2 gives a comparison of the blood pH with the sedimentation test and leucocytic index.

TABLE 2

AGREEMENT	FAVORABLE	STATIONARY	UNFAVORABLE	TOTAL	PERCENTAGE
pH, sedimentation test and leucocytic index	17	0	2	19	31
pH and sedimentation test	26	2	6	34	55.8
pH and leucocytic index	23	0	5	28	46
Sedimentation test and leucocytic index	24	1	9	34	55.8
No agreement				3	5

RELATION BETWEEN THE pH OF THE BLOOD AND SEDIMENTATION TEST AND LEUCOCYTIC INDEX ON ADMISSION AND DISCHARGE EXAMINATIONS

This study showed that there was no apparent relationship between the pH of the blood and the normality or abnormality of the two other tests. In other words, the leucocytic reaction and the sedimentation rate of erythrocytes do not appear to be affected by the relatively slight change in the pH values of the blood. Table 3 is a compilation of these tests on admission and on discharge to compare the normal, alkaline and acid pH values with the other two tests.

TABLE 3

		SEDIMENTATION TESTS		LEUCOCYTIC INDEX		GENERAL TREND	
		Normal	Pathological	Below 26	Above 27	Sedimentation test normal	Index equal −26
Admission examinations of patients							
Normal pH	28 (46%)	19 (68%)	9 (32%)	11 (39%)	17 (61%)		
Alkaline pH	30 (49%)	19 (63%)	11 (37%)	11 (37%)	19 (63%)	40 (66%)	23 (38%)
Acid pH	3 (5%)	2 (66%)	1 (33%)	1 (33%)	2 (66%)		
Discharge examinations of the same group							
Normal pH	29 (47.5%)	18 (62%)	11 (38%)	14 (48%)	15 (52%)		
Alkaline pH	29 (47.5%)	24 (83%)	5 (17%)	19 (66%)	10 (34%)	44 (72%)	35 (57%)
Acid pH	3 (5%)	2 (66%)	1 (33%)	2 (66%)	1 (33%)		

A COMPARISON OF pH OF BLOOD AND COMPLEMENT FIXATION TEST FOR TUBERCULOSIS

In this comparison both positive and negative complement fixation tests were found in the acid, normal and alkaline blood. Some weakly

positive tests became strongly positive and some negative tests became positive when the pH of the blood became less alkaline. Among these cases there were eighteen which had stronger reaction on discharge than on admission. The pH of the blood of these cases on discharge was as follows: three were normal and stationary; nine showed decreased

TABLE 4 (A)

Distribution of positive and negative complement-fixation tests

	++++ & +++	++	Negative
Admission, min.	9 (32%)	11 (40%)	8 (28%)
Discharge, min.	13 (46%)	11 (40%)	4 (14%)
Admission, M.A.	12 (52%)	4 (17%)	7 (30%)
Discharge, M.A.	15 (65%)	4 (17%)	4 (17%)
Admission, F.A.	8 (80%)	0	2 (20%)
Discharge, F.A.	8 (80%)	1 (10%)	1 (10%)
Admission, total	29 (47.5%)	15 (24.6%)	17 (27.9%)
Discharge, total	36 (59%)	16 (26%)	9 (15%)

TABLE 4 (B)

Distribution of positive and negative complement-fixation tests among the different pH groups

		COMPLEMENT-FIXATION TESTS			GENERAL TREND IN WHOLE GROUP		
		++++ & +++	++	Negative	++++ & +++	++	Negative
Admission examinations							
Normal pH. . .	28	13 (46.5%)	8 (28.5%)	7 (25%)			
Alkaline pH. . .	30	15 (50%)	7 (23.5%)	8 (26.5%)	29 (48%)	15 (24.6%)	17 (27.9%)
Acid pH.	3	1 (33.3%)	0	2 (66.6%)			
Discharge examinations							
Normal pH. . .	29	16 (55.5%)	8 (27.5%)	5 (17%)			
Alkaline pH. . .	29	18 (62%)	7 (24%)	4 (14%)	36 (59%)	16 (26%)	9 (15%)
Acid pH.	3	2 (66.6%)	1 (33.3%)	0			

alkalinity; five, were more alkaline; and one changed from acid to alkaline. Five cases had a weaker complement fixation test on discharge. The pH of the blood in these cases was as follows: three were normal and stationary; two showed a slight decrease of alkalinity. Eight cases had negative complement fixation tests on admission and on discharge. The

pH of the blood was as follows: two were normal and stationary; four had decreased alkalinity; two had changed from acid to alkaline. On the whole there is no appreciable difference in the percentages of positive and negative complement fixation tests among the normal, alkaline and acid groups.

Table 4 (A) & (B) gives a comparison of the pH of the blood and the complement-fixation tests on admission and discharge.

DISCUSSION

It is generally recognized that the blood is a very complex, highly buffered tissue, which is very sensitive to change, especially when removed from its natural environs. Because of this sensitivity to an altered environment it is generally conceded that an absolutely true pH of the blood is very difficult, if not impossible, to obtain. To eliminate any great change Havard and Kerridge (4) advocated the determination of the pH within two minutes after withdrawal of the blood. They found, however, that with the blood placed under oil there is not sufficient pH change within two hours after removal at room temperature to prevent a reliable relative pH being obtained. In the report here given the same person did all of the tests, using the same technique for all blood samples. A variation from pH 7.20 to 7.485 in different individuals has been found. Repeated tests have shown that in many the pH has been fairly constant, while in others there has been considerable change. We believe that with a uniform technique reliable results can be obtained.

Text-books of physiology and biochemistry (5) give the pH range of the blood in health as from 7.34 to 7.5. Can this be regarded as correct? If so, then in over 95 per cent of the cases, which we have examined and in which disease was evident, there was no alteration of the pH of the blood from that of a normal healthy person.

Ely (6), using the technique of Hastings and Sendroy found that the pH of normal blood varied from 7.35 to 7.39, with an average of 7.37. Using the same method, we found the variation from 7.35 to 7.41, with an average of 7.384 in our control group. Fosbinder (7) contends and our experience agrees that the pH range given for health is too broad. In our present report we have arbitrarily placed the pH limit of normal between 7.37 and 7.39. Values below this we have considered as acid and above as alkaline. We recognize that these values may be too arbitrary.

The pH values found in grave tuberculosis cases showed a considerable range. In a few instances the pH of the blood was determined a few hours before death. In all these, the values were on the acid side, the lowest determination being 7.20. Strict bed-cases gave definitely more alkaline reactions than did the ambulatory cases. In a general way, it was found that the pH values of all patients tended to be less alkaline near the time of discharge than at the time the first test was done after admission. As a rule our first test was done one day to a week after admission, and during this time no exercise was allowed. The discharge examination was done when the patients became accustomed to from two hours to unlimited exercise, after a few months' to two years' residence in the sanatorium.

The above observations led to the determination of the pH of the blood before breakfast, and then on the same individuals in the afternoon after considerable exercise had been taken. The values obtained in the afternoon were distinctly less alkaline than the morning values. Several early morning pH values on two sheep were determined; the sheep were then strenuously exercised for a considerable length of time, after which blood was drawn and the pH determined. The following results were obtained:

Sheep	*Before exercise* pH	*After exercise* pH
1	7.35	7.275
2	7.395	7.295

From these observations one is led to the conclusion that exercise alone can alter the pH values of the blood.

McDonald and his co-workers (8) have found that the majority of cancer patients have a pH value of 7.40 or more. DesLigneris (9) reported that fowl with malignant tumors have more alkaline blood than do normal fowl. Recently, a report by Dickinson and Havard (10) calls attention to the fact that cachectic patients show relatively alkaline pH values. Is it possible that this alkalinity in cancer patients may be due to cachexia and to a lessened physical activity? From our experience we are led to doubt any specificity of the high pH values in malignant tumor. During this study the lowest pH of the blood was found in a case of ovarian cyst; chronic arthritis and some duodenal ulcer cases also had low pH values. The highest pH values were found among the patients with generalized arteriosclerosis and one with chronic colitis.

SUMMARY

1. The pH accepted as normal for health appears too broad.

2. To obtain basic and comparable pH values we suggest taking a fasting blood early in the morning. This is especially important since we have found that exercise affects the pH values.

3. The pH values of the blood of ambulatory tuberculosis patients do not vary significantly from the values obtained in nontuberculous cases and in normal controls. Strict bed-cases have, as a rule, more alkaline blood than ambulatory cases.

4. No definite correlation between the pH of the blood, sedimentation rate of erythrocytes, the leucocytic reaction, and the complement-fixation test for tuberculosis was found.

REFERENCES

(1) HASTINGS AND SENDROY: Colorimetric determination of blood pH at body temperature without buffer standards, Jour. Biochem., 1924, lxi, 695.

(2) CRAWFORD AND MEDLAR: Further studies of leucocytic reaction in tuberculosis, Amer. Rev. Tuberc., 1935, xxxi, 611.

(3) MEDLAR: An evaluation of the leucocytic reactions in the blood as found in cases of tuberculosis, Amer. Rev. Tuberc., 1929, xx, no. 3.

(4) HAVARD AND KERRIDGE: An immediate acid change in shed blood, Biol. Jour., 1929, xxiii, no. 4.

(5) WRIGHT: Applied physiology, Oxford Publication, 1932, p. 23.
PETERS AND VAN SLYKE: Quantitative clinical chemistry, Williams & Wilkins Co., Baltimore, 1931, p. 941.

(6) ELY: Studies on the hydrogen-ion concentration of the blood in cancer, Amer. J. Cancer, 1933, xvii, no. 1.

(7) FOSBINDER AND SCHOONOVER: A comparison of colorimetric and electrometric methods for the determination of the pH of serum or plasma, Biochem. Jour., 1930, xxiv, no. 6.

(8) MCDONALD: Cellular division in relation to cancer, Science, February 15, 1929, lxix, no. 1781.

(9) DESLIGNERIS: Hydrogen-ion concentration of fowl's blood in Rous' sarcoma and in infections avian tuberculosis and salmonellosis, Brit. Jour. Exper. Path., 1932, xiii, 189.

(10) DICKINSON AND HAVARD: The reaction of arterial blood in cancer, Ibid., 1933 xiv, no. 6.

THE BIOLOGICAL EFFECTS OF BERYLLIUM

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In the course of a comprehensive investigation of the chemotherapy of experimental tuberculosis in guinea pigs initiated by the late Dr. W. H. Bucher and Dr. Lawrence E. Wright at Olive View in August, 1926, a systematic study of the inorganic substances was undertaken. Accordingly salts were prepared of all obtainable elements and administered to tuberculous guinea pigs, and the course of the tuberculosis under such treatment carefully observed. Elements studied in this manner included aluminum, antimony, arsenic, barium, beryllium, bismuth, boron, bromine, cadmium, caesium, calcium, carbon, cerium, chlorine, chromium, cobalt, copper, fluorine, gold, hydrogen, iodine, iron, iridium, lanthanum, lead, lithium, magnesium, manganese, mercury, molybdenum, nickel, nitrogen, osmium, oxygen, palladium, platinum, phosphorus, potassium, rhodium, rubidium, ruthenium, selenium, silicon, silver, sulphur, strontium, tantalum, tellurium, thallium, thorium, tin, titanium, tungsten, uranium, vanadium, yttrium, zinc, and zirconium.

The methods used and results obtained in general have been described in a previous publication. Briefly, five guinea pigs, each weighing over 400 gm., and previously free of tuberculosis, were injected with small doses, usually 0.000,1 mgm. of a virulent strain of tubercle bacilli, human type, known as *H98*, that had been stable for several years in this laboratory. Injections of neutral solutions of the above listed substances were given subcutaneously, usually three times a week, in doses just below the maximum tolerated amount, and in some smaller fraction of this dose. At the end of ninety days the animals were killed, and the extent of tuberculosis determined macroscopically and compared to that of a set of controls inoculated in the same manner in terms of a fixed set of standards, which have been previously described in greater detail (1).

Although no substance was found that would exert a definitely favorable influence on the course of the experimental tuberculosis in guinea pigs, the investigation has not been abandoned, but is now being continued with various types of organic compounds. The totally unex-

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pected discovery was made, however, that it was possible by this means to enhance the pathological process developing in these animals, and it is with this phenomenon that the present report is concerned.

In the course of this study, *Beryllium* (2) (sometimes called *Glucinium*), the light bivalent metallic element of atomic weight 9 and atomic number 4, was first used in the form of the basic tartrate in March, 1928, in doses of the salt corresponding to 0.2 and 1.0 mgm. Be. The 10 animals so treated showed nearly 30 per cent more tuberculous lesions than were present in the untreated controls. About a year later, the experiment was repeated, using the chloride of beryllium in doses of 1 and 5 mgm. Again the treated animals showed approximately 50 per cent more tuberculosis than did the controls.

TABLE 1

Beryllium chloride

Treatment given subcutaneously: repeated weekly or more often: infection, H98, 0.0001 mgm., subcutaneously: duration of experiments, three months after infection

NUMBER OF GUINEA PIGS TREATED	DOSE OF TREATMENT IN MGM.	AVERAGE TUBERCULOSIS PER GUINEA PIG TREATED	AVERAGE TUBERCULOSIS PER GUINEA PIG CONTROLS	AVERAGE DIFFERENCE
86	10	10.6	6.4	+4.2
15	5	13.1	7.3	+5.8
10	1	7.5	6.7	+0.8
10	0.1	7.4	6.1	+1.3
10	0.01	8.7	7.2	+1.5
20	0.001 to 0.00,001	8.3	6.6	+1.7

Although at first this acceleration of the development of tuberculosis in the treated guinea pigs was suspected of being just a chance coincidence, further experimentation has demonstrated beyond a doubt that it is a constant effect of the treatment with the salts of beryllium.

More than 500 different infected guinea pigs have been given injections of beryllium, usually in the form of weekly injections of the opalescent neutral solution, containing 10 mgm. of the basic beryllium chloride, and a somewhat greater number of guinea pigs have been observed without such treatment as controls. On the average, the guinea pigs so treated have developed 4 units (on our scale of 0 to a possible maximum of 16) more tuberculosis than have the untreated controls, or an increase of about 50 per cent (table 1).

This is especially remarkable, since in the course of the entire series of

experiments with the other 59 elements, and a greater number of organic compounds and dietary or other environmental factors, involving more than 5,000 guinea pigs, no such aggravation of the tuberculosis could be induced, the only agent consistently causing a marked increase in the extent of the tuberculosis being the salts of beryllium. A few other agents causing a slighter and less constant increase, as well as a few causing slight apparent decreases, both within the range of chance variation, are still being investigated.

When it had become apparent that the injection of beryllium salts caused an increase in the amount of tuberculosis developed, studies were made of the condition under which this occurred. It was found to occur as well whether the guinea pigs had been inoculated with large or with small doses of virulent human bacilli (table 2), and whether the infec-

TABLE 2

Beryllium chloride

Treatment given subcutaneously: repeated weekly or more often: infection, H98, varying doses, subcutaneously: duration, three months after infection

NUMBER OF GUINEA PIGS TREATED	DOSE OF TREATMENT IN MGM.	DOSE OF INFECTION IN MGM.	AVERAGE TUBERCULOSIS PER GUINEA PIG TREATED	AVERAGE TUBERCULOSIS PER GUINEA PIG CONTROLS	AVERAGE DIFFERENCE
5	10	1.0	14.8	13	+1.8
10	10	0.01	12.6	9.7	+2.9
10	10	0.00,001	11.2	5.3	+5.9
5	10	0.000,001	8.4	4.8	+3.6
5	10	0.000,000,1	7.2	2.4	+4.8

tion was administered subcutaneously or by inhalation, and whether the animals were killed off in six weeks or three months or allowed to go on to death. Other virulent tubercle bacilli besides the *H98* strain also gave increased lesions with beryllium, but administration to animals infected with avirulent organisms, like *BCG* or KI were without effect (table 3).

Oral administration of the beryllium did not appear to be effective. The single injection of one dose, or a few doses of beryllium, or its repeated injection for a short time after the infection were usually ineffective, but repeated injection after the infection had already developed did cause increased lesions. Small doses seemed to give less constant results than the larger doses (3).

Admixture of beryllium with the tubercle bacilli did not appear to

TABLE 3

Beryllium chloride

Treatment, subcutaneous, varying dosage; infection, subcutaneous, various organisms; duration, varying time

NUMBER OF GUINEA PIGS TREATED	DOSE OF TREATMENT IN MGM.	NUMBER OF DOSES PER GUINEA PIG	INFECTION	DOSE OF INFECTION IN MGM.	DURATION OF EXPERIMENT	AVERAGE TUBERCULOSIS PER GUINEA PIG TREATED	AVERAGE TUBERCULOSIS PER GUINEA PIG CONTROLS	AVERAGE DIFFERENCE
15	1–10	46	B1	0.000,1	3 Mo.	3.8	4.0	−0.2
5	10	14	BCG	10	3 Mo.	0.2	0	+0.2
5	10	14	K1	10	3 Mo.	0.6	0	+0.6
10	2–10	49	H98	0.000,1	To death	13.7	12.6	+1.1
5	10	9	H98	0.000,1	1½ Mo.	5.6	3.8	+1.8
40	10–100	1	H98	0.000,1	3 Mo.	7.1	6.5	+0.6
15	5–10	2–7	H98	0.000,1	3 Mo.	8.8	7.4	+1.4
130	10	12	Diagnostic material		2 Mo.	6.7	5.8	+0.9
			Spray					
5	10	24	H98	0.01	3 Mo.	12.2	9.6	+2.6
	Oral							
15	10–100	71	H98	0.000,1	3 Mo.	8.4	10.6	−2.2

TABLE 4

Beryllium compounds other than chloride

Treatment, subcutaneous and inhalation; infection, H98, 0.000,1 mgm., subcutaneous; duration of experiments, three months

COMPOUND	NUMBER OF GUINEA PIGS TREATED	DOSE OF TREATMENT IN MGM.	AVERAGE TUBERCULOSIS PER GUINEA PIG TREATED	AVERAGE TUBERCULOSIS PER GUINEA PIG CONTROLS	AVERAGE DIFFERENCE
Nitrate	15	10	8.4	7.0	+1.4
Nitrate	5	0.5	8.0	7.2	+0.8
Phosphate	5	10	9.4	6.2	+3.2
Lactate	5	20	13.2	6.2	+7.0
Citrate	10	0.3	6.6	6.9	−0.3
Tartrate	5	14	11.6	8.0	+3.6
Tartrate	5	7	11.0	9.6	+1.4
Tartrate	10	3	10.7	8.8	+1.9
Carbonate*	5	100	3.2	2.8	+0.4
Oxide	5	Spray daily	9.6	9.6	0
Oxide†	5	Spray daily	1.8	1.6	+0.2

* Infection: B1, 0.000,1 mgm. subcutaneously.

† Infection: H98, 0.1 mgm. by inhalation.

affect their growth on culture, nor its admixture in the artificial culture medium used. No effect was observed on the course of experimental tuberculosis in rabbits inoculated with human tubercle bacilli.

The infected guinea pigs given beryllium developed positive skin tests about the same time as the controls, but the reactions were sometimes more marked, and the lymph nodes were often larger in the same length of time. The weight-curve on the infected animals showed more loss of weight than the controls, coincident with the spreading disease.

Various compounds of beryllium were observed (table 4). The basic chloride, the nitrate, the tartrate, the phosphate and the lactate all gave similar results. The citrate and a suspension of the insoluble carbonate gave no perceptible effect. This may, perhaps, be connected with the fact that in the citrate the beryllium is so bound as to be less ionized. The soluble salts, however, were all much more toxic than the insoluble or colloidal ones; thus 25 mgm. of the opalescent beryllium chloride could be administered with only a local irritation, while only 0.5 mgm. Be as the tartrate or 0.2 mgm. Be as the citrate could be given, without killing the animal (4).

Beryllium administered to normal animals in sublethal doses had little effect on their general health, weight-curve or blood count. The beryllium rickets reported in rats on diets containing large amounts of beryllium were not observed in these guinea pigs (5). The mechanism of the effect of beryllium on tuberculosis is unknown, but some effect appears certain.

A practical application of these findings has been made in the use of beryllium routinely in the diagnostic tests for tuberculosis in sputum, urine, etc., on guinea pigs. During the past three years more than 300 specimens of such materials suspected of containing tubercle bacilli were administered to pairs of guinea pigs, one of which also received weekly injections of 10 mgm. beryllium chloride. Viable tubercle bacilli were present in 130 of these specimens, although all were negative by the ordinary smear method, as shown by the development of tuberculosis in the guinea pigs. In most instances the two animals injected with the same material showed similar amounts of tuberculosis, but in 76 animals the one treated with beryllium showed more tuberculous lesions on autopsy, while in only 42 was the reverse true. Seven of the beryllium-treated animals showed tuberculosis while the controls were negative, as compared to only three instances in which the nontreated animals showed tuberculosis and the treated ones were negative. This may, of course,

have been mere coincidence, but it appears probable that, in view of our experimental results, we actually discovered 4 more cases net because of the beryllium than would have been found if only the nontreated animals had been used.

The practical value of this procedure is, as yet, of little moment. On the other hand, we feel that the demonstration that the course of tuberculosis in the guinea pig can be consistently affected, even in an untoward direction, by the administration of such an agent is of greater theoretical significance and gives encouragement to further studies in chemotherapy.

REFERENCES

(1) BOGEN, E.: Experimental tuberculosis in guinea pigs, Tr. Nat. Tuberc. Assoc., 1932, xxviii, 163.

(2) PARSONS, C. L.: The Chemistry and Literature of Beryllium, 1909.

(3) WALBUM, L. E.: Therapeutic experiments with metal salts. Experiments with tuberculosis, Acta. Path. Microbiol. Scand., 1926, iii, 489.

LUNDE, N.: The treatment of phthisis with small doses of metal salts, Tubercle, 1926, viii, 103.

(4) GIES, W. J.: Experiments with salts of aluminum and beryllium, J. Pharm. & Exp. Therap., 1911, ii, 403.

SEAMAN, EMILY C.: Biochemical studies of beryllium sulphate, Columbia Univ. Dissert., 1912, Biochem. Bull., ii, 184.

(5) BRANION, H. D., GUYATT, B. L., AND KAY, H. D.: Beryllium rickets, Jour. Biol. Chem., 1931, xi, 92.

THE UNDERGRADUATE TEACHING OF TUBERCULOSIS

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It is my plan to approach the question of the undergraduate teaching of tuberculosis to medical students as a part of the course in internal medicine and to a lesser degree also surgery, rather than from the point of view of a specialty in medicine.

The idea that tuberculosis is a systemic infection which develops clinical manifestations in practically all organs of the body, and therefore important in all branches of medicine, should constantly be borne in mind, but, as it is in the lungs that tuberculosis is seen most frequently, it is to education in this phase of the disease that we shall chiefly address ourselves.

Physical and Roentgenological Diagnosis: It is generally conceded that at graduation the usual medical student has a very inadequate appreciation of the problems of tuberculosis, and that his preparation for the diagnosis and treatment of the disease is far from satisfactory. Students first come in contact with cases of pulmonary tuberculosis through the clinical material employed for the teaching of physical diagnosis. This approach appears to give many of them the lasting impression that the physical signs are of predominant importance in the recognition of the disease. As a matter of fact, the physical signs in such cases are usually those of lesions already far advanced, and while these cases afford ideal clinical material for the demonstration of the varied physical signs which may be present in the chest, they give a one-sided picture of the disease as a clinical entity and interfere with progress toward earlier diagnosis which is the most important medical approach to the control of pulmonary tuberculosis. The emphasis placed upon physical examination, important as this is, cannot attain this desired object for the reason that early diagnosis of pulmonary tuberculosis cannot be achieved by improved skill in physical examination of the chest, but rather by a well-balanced appreciation of the importance of the detailed clinical history and, on

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examination, by proper interpretation of the roentgenogram. It is now being generally recognized, as Braeuning has well put it, that early pulmonary tuberculosis must be seen, not heard. This means that a much greater emphasis than at present should be placed upon the study of roentgenograms of the chest, and that the limitations of physical examination of the chest should be better recognized. It would appear desirable from the very first contact of the student in his second year with pulmonary tuberculosis that in connection with the teaching of physical diagnosis there should be emphasized its correlation with the corresponding pathological conditions at autopsy and the study of the pathological changes during life, which is afforded by the roentgenogram.

Study of the Course of the Disease as a Whole: Another very definite failing in the present situation is the lack of appreciation of the variegated course which pulmonary tuberculosis may run. Students as a rule have little opportunity to watch the course of any individual case over a period of time. Such opportunity is essential if they are to understand the pathogenesis and evolution of the infection which leads to its varied clinical manifestations. The remedy for this would be wider opportunity for the prolonged study of cases in an institution such as a sanatorium, in addition to the material which is available in an acute hospital service which is designed primarily for diagnosis and for transient care.

The course of the disease may however be very satisfactorily taught by means of serial roentgenograms correlated with the associated clinical symptoms. Tuberculosis must be thought of as a dynamic, moving clinical picture rather than as a static condition. The fixed methods of classification in vogue have probably interfered not a little with the appreciation of this conception.

Chronic versus Acute Disease: Another failing in the training of the student is shared with many other diseases. I refer to the natural reaction of any student to be overimpressed with the importance of the more dramatic acute conditions and, in consequence, to lack an enthusiastic interest in chronic disease. The remedy for this condition would appear to depend largely upon the skill and enthusiasm of the teaching staff. Under proper leadership the student may be thrilled by the satisfaction of achieving a correct diagnosis by the meticulous study and correlation of slight, often apparently inconsequential pieces of evidence, quite as much as by the results of an exploratory laparotomy. At the same time,

the satisfaction of successful treatment over many months in the face of innumerable small difficulties can be demonstrated to be quite equal to that following the successful outcome of the treatment of a case of acute pneumonia.

The close personal relationship established between physician and patient is also the best sort of training for the development of that broad understanding which we like to think of as one of the most admirable qualities of our profession. Nowhere can this be developed so well as in the management of chronic disease such as tuberculosis, demanding as it does a full knowledge of all the personal, social and economic factors involved, as well as a close scrutiny of many symptoms which are often slight and which require painstaking study to appreciate their significance.

General Training for Teaching Staff: In order to place before the student the necessary clinical material in a proper way, a special chest service and a properly trained staff is of course essential. It is my strong feeling, however, that this service should be very closely integrated with that of internal medicine, and that the members of the staff should not be alone specialists in chest diseases but should also have a broad fundamental experience in general medicine.

Correlation of Other Chronic Chest Diseases with Tuberculosis: Also, because of the fact that the study of pulmonary tuberculosis affords the opportunity for special training in chronic diseases of the lungs which are not tuberculous, I would strongly emphasize the importance of a general chest service for chronic pulmonary disease, including such diseases as pulmonary emphysema and fibrosis, bronchiectasis, pulmonary abscess, pneumonoconiosis and malignant diseases of the lung, with, of course, provision for proper segregation of the tuberculosis cases. This results in the better training in differential diagnosis, the better treatment of nontuberculous chronic chest conditions and also in a broadening of the basis of interest on the part of the attending staff as well as of the student.

Incidental General Medicine: If we add to this material the very numerous incidental medical and surgical complications which occur in the course of tuberculosis and the incidental complicating general diseases which are bound to occur in any such service, we have offered to us a wide

variety in the teaching material available for students, which, if properly studied and properly taught, deserves to have such a service rank in importance with the regular general medical service in the assignment of teaching hours for the undergraduate student. If there be added to this the opportunity for a few days of intensive study in a neighboring sanatorium to learn the details of the sanatorium methods of treatment and the wide variety in the course of the disease, we have a very satisfactory teaching set-up for bed-cases.

Out-Patient Teaching: Social and Preventive Aspects: In addition to this, however, we have an immense clinical material available for the study of ambulatory cases in the out-patient department. Here, too, the special tuberculosis clinic should include the other chronic chest diseases, and it is here that the opportunity for the teaching of early diagnosis is afforded and the follow-up after-care so important in the management of any chronic disease, particularly tuberculosis, where the behavior of patients after they return to normal environment and normal working and social conditions is most helpful, both for the better understanding of the disease and for the best interests of the patient. But even more important than this, the out-patient department affords the opportunity for application of the modern principles of preventive medicine, and this is linked very closely with the social problems of medicine.

Tuberculosis has afforded one of the chief bases for the recent rapid development of the necessary technique in the prevention of disease and in the appreciation of the associated social problems, but as yet rarely has preventive or social medicine been thoroughly taught to the undergraduate medical student. If I read the signs of the time aright, it is in this direction that especially exacting demands are to be made upon the next generation of practitioners in medicine who are too frequently graduated with a dominating interest in curative medicine. The tuberculosis clinic affords an ideal training ground for this purpose.

The organized efforts for the prevention of tuberculosis through our public-health agencies as well as numerous coördinated private agencies, and the methods of health surveys as a foundation for preventive health examination are too little known by the medical student and consequently by the younger practitioner. They are learned only slowly and inadequately later by experience in private and hospital practice. The underlying principles involved can be taught to the student systematically in the tuberculosis clinic. In a properly coördinated program of teaching,

the department of preventive medicine and hygiene as well as the departments of social service and economics should be associated with the department of internal medicine, and also the public and private resources of the community should be studied.

Some efforts along these lines are already being made in some medical schools, but they are still sporadic and inadequate. Properly developed, this combined medical, public-health and social approach to the problem would lead to a broadening of the whole basis of the understanding of the students of the social background, so important in many diseases, the many home and economic elements involved, and would also impress upon them their responsibility for an understanding of the methods of spread of the disease, and consequently their responsibility for its prevention as well as for its treatment. Through the social-service department each student should have an opportunity to carefully visit and study on the ground the homes and working places of a few patients under their care, and to study the public-health aspects of the problem as developed by examination of contacts, particularly children, the importance of untoward environment and the possibilities of its remedy.

Psychological Studies: Another important aspect of the problem is the psychological one. The rapid advance in scientific medicine has tended to emphasize the importance of exact scientific data. The problems that can be solved by scientific proof in the laboratory or by modern clinical methods of study have a very natural appeal to the student or physician with scientific training. Efforts to reduce all problems as far as possible to the realm of demonstrable facts should of course be thoroughly encouraged. On the other hand, there is an art as well as a science of medicine, and in the practice of this art it is the personal intangible factors not susceptible to scientific analysis which are important. The field of chronic disease, and perhaps particularly tuberculosis, offers extraordinary opportunities for the development of this art. Any patient with chronic disease faces a great psychological and emotional problem as well as a physical one. Too often physicians fail to appreciate this. Too little have they been trained to make the most of their opportunities to help their patients with this phase of their problem. The development of innumerable cults stressing the mental, psychological and emotional factors in the treatment of disease is the direct response to the need of these patients, and to a considerable extent is an evidence of the failure of the medical profession to meet this need properly. If the physi-

cian of tomorrow is to improve upon this situation, the student of today should be thoroughly acquainted with the importance of these intangible problems, and much more effort should be made to improve him in the technique of their management. Some individuals have a natural gift in this direction,—the much talked-of old family physician usually had it. But in most medical students it has to be developed, and if, as at present, its importance is not even recognized and no concerted effort is made to present it, it is not to be wondered at that the tangible scientific aspects of our medical problems dominate the situation in their minds, to the exclusion of those which are more personal and intangible.

I should like to see the psychologist and psychiatrist more closely linked to the group which is to coöperate in the training of the student in the care of chronic illness.

Teaching of Pathology: Of course, in tuberculosis, as in every branch of medicine, the study of the pathological conditions involved is essential. The coördination of the pathological findings at autopsy with the clinical data by means of pathological-clinical conferences and other methods of demonstration is most helpful. In tuberculosis it is particularly important to trace as far as possible the evolution of the pathological processes, as opposed to a simple analysis of the pathological end-result. The concept of this disease as a changing picture rather than as a fixed entity is thus emphasized, and a better appreciation of its pathogenesis is obtained.

Tuberculosis in Children: Nowhere is this line of study more fruitful than in the case of children, at which age first tuberculous infections most frequently occur. Many recent advances in our knowledge of the disease have been made possible by carefully combined pathological and clinical studies of tuberculosis as it manifests itself in children, and this has led to a better understanding of the later adult forms of the disease. Thus does the study of pulmonary tuberculosis again cut across artificial barriers in the curriculum, and the pediatrics service comes to be closely correlated with the chest service, and in an ideal set-up a children's division of the chest service is to be recommended.

Surgical Aspects: So it is in surgery also. The treatment of pulmonary tuberculosis has been revolutionized by modern collapse methods, beginning with artificial pneumothorax and going on to include the various more radical surgical procedures. The principles of modern thoracic

surgery are largely based upon experiences in pulmonary tuberculosis and similar chronic infections. It has developed upon a sound basis only if there is a very close coöperation between the surgeon and the internist. Medico-surgical conferences and teaching-clinics have done much to foster the mutual dependence of the surgeon and the internist; and to the student who may have surgical inclinations there is thus afforded an opportunity to learn the relative value of surgical procedures and other parts of the program of treatment in which the surgical operation itself is only one episode.

To my mind one of the many important by-products of the progress in modern chest surgery has been the development of an interest upon the part of surgeons in the problems of chronic disease, especially tuberculosis, and when this interest is stimulated during impressionable student days the effect may be very far-reaching upon the future practice of medicine.

It is suggested, therefore, that a chest service should have its closely correlated surgical unit and that the student should have an opportunity to study the course and treatment as a whole under the combined guidance of both the internist and the surgeon.

Place in the Curriculum: The amount of time that should be allotted in the curriculum for the study of pulmonary tuberculosis and allied chronic chest conditions would depend very largely upon the degree to which all of the conditions suggested as desirable in a chest service are fulfilled. If they are all available, then not a little of the time which is assigned to the student for the study of internal medicine could be allotted to the chest service, inasmuch as special training in chest diseases and in general medicine could go hand in hand. In most services and teaching institutions such a complete service as we have suggested is not available and consequently modifications of the teaching program would be necessary to fit local conditions.

In general, it would seem as though we should begin the 2nd and 3rd year of the medical students' life with a somewhat different approach to chest diseases, emphasizing of course physical diagnosis, but also enabling them to understand the limitations of this one method of procedure. Also, during this phase of training it would seem logical to begin to include X-ray and pathological material in order to coördinate them with the physical signs; and, all through the entire course, much more training in the interpretation of roentgenograms should be afforded than now exists

in most medical schools. The time is gone by when the practitioner in medicine would be satisfied to accept the report of the roentgenologist as giving him a full interpretation of the knowledge to be obtained by this important method of examination.

It would seem, however, to be evident that it is in the 4th year, during the period of so-called medical clerkship, that most of this teaching material on chest diseases should be placed before the undergraduate student. Each such student should certainly at least have one month, and preferably six weeks, of continuous all-day study, with a schedule including all of the various angles of approach that we have suggested.

The Bellevue Hospital Service: This comprises 180 beds, mainly for tuberculosis, but between 15 and 20 per cent of all patients are suffering from chronic nontuberculous chest conditions. The service is quite active, there being over 3,000 admissions each year. For teaching, it is organized primarily as a part of the Department of Medicine of the College of Physicians and Surgeons, but because of the unique character of this Service and because both the New York University and Cornell Medical Schools also use Bellevue Hospital largely for teaching, it has been arranged to share the advantages of this Service between these three medical schools, so that the students as well as the internes and visiting staff from all three divisions share in the Service which, however, remains under the immediate control of the College of Physicians and Surgeons.

There is a salaried resident staff of 6 physicians, who have already had a regular interneship in internal medicine, with a chief resident physician at their head. Internes from the medical services of the three divisions rotate in the Tuberculosis Service for varying periods of service. This group of resident and interne physicians is afforded an opportunity for postgraduate training, and a great majority of the physicians who are now specializing in chest diseases in New York City are those who have been through this Bellevue Service.

The visiting staff is under the usual part-time arrangement, with also a plan for rotation between the regular visiting staff of the Tuberculosis Service and that of the General Medical Service. The executive medical supervision is exercised by a full-time visiting physician, Dr. J. Burns Amberson, Jr., to whom the success of our teaching program is very largely due.

A very large out-patient clinic and a day-camp are integral parts of the Service. All members of the visiting staff and some of the resident staff take part in the undergraduate teaching.

Each *P. & S.* fourth-year student is required to spend $3\frac{3}{4}$ weeks full-time in this Service. In the New York University a very popular elective course of four weeks is offered to the fourth-year students. Cornell University does less teaching than the others but has plans to do more in the near future. About 150 fourth-year undergraduate students pass through this Service each year.

General Plan of Instruction: At the beginning of each year all of the fourth-year students of the three medical schools are excused from all other exercises and attend three full days of lectures, which is known as the tuberculosis symposium. The various phases of tuberculosis as this occurs in the various branches of medicine and surgery are outlined at this time, the object being to inculcate the idea of the unity of tuberculosis as a systemic disease, and to make more effective the incidental teaching of tuberculosis which is included in the various special courses during the year.

With this introduction the *P. & S.* student comes to Bellevue in groups of ten and twelve for his period of $3\frac{3}{4}$ weeks of intensive tuberculosis training. This group is broken up into smaller groups, of not more than 4 students each, for individual bed-side instruction and out-patient teaching, with special emphasis upon early and differential diagnosis, and with great emphasis upon the use of the X-ray both by fluoroscopy and the roentgenogram. This is greatly facilitated by the fact that we have our own separate roentgenological installation for this Service, and all of the films are kept filed with the current clinical records and are convenient for the use of the visiting staff and for the students.

The students are also taught individual clinical laboratory procedures, have special instruction in the pathology of tuberculosis in small sections, and attend several autopsies. They also have the opportunity to follow special studies that we are making in the field of functional pathology, a difficult phase of medicine which however is becoming increasingly important for the proper understanding of many chest conditions and is particularly valuable in pulmonary tuberculosis, as affording a better basis for the selection of cases suitable for radical surgery.

They also receive instruction in special procedures, such as in examination of the larynx, bronchography and particularly artificial pneumothorax.

Each student also spends three afternoons in the out-patient clinic, which affords him the opportunity for training in early diagnosis and also

an insight into the social and preventive aspects of tuberculosis. In the comparatively near future this training will be greatly facilitated by University participation in the proposed Health Centers in the City of New York. Eighteen such Centers are planned by the Department of Health, four of which will be connected with, and under the medical control of, the Departments of Preventive Medicine in the four larger medical schools, thus affording splendid opportunities not only for the teaching of undergraduates but also for the training of graduates in preventive medicine, including tuberculosis.

At frequent intervals the entire group of students is brought together for special short lectures, including clinics arranged to demonstrate the particular subject covered in each lecture. They also attend a pathological-clinical conference each week, a medical-surgical conference and a staff conference. These conferences are for the benefit of the visiting and resident staff primarily, and consequently often present problems too advanced for ordinary undergraduate teaching. But it has been found that much advantage accrues to the students from the opportunity to listen to these discussions between the older men and to participate in them freely by questions or suggestions. The conferences also afford a means for directing student's attention to methods of clinical research and the manner in which the older men, who are still students as well as practitioners, develop and crystallize their ideas.

In addition to this, the students are encouraged to use the library, and a specially trained member of the staff in a conference each week aids them in the methods of utilizing the literature and stimulates their interest in searching original sources of information concerning the various cases which they are studying.

Each group of students has the opportunity to spend one week-end each month at the Loomis Sanatorium, which has been found to be a very profitable and popular experience.

It can thus be seen that we have provided at Bellevue many of the basic requirements which I have outlined as desirable for teaching tuberculosis to undergraduates. We still lack our own Children's Service and our own special Surgical Service. Both of these will however be provided in plans for the new building which will be completed in about two years.

We also wish to develop more completely, in coöperation with the Department of Preventive Medicine, the social and preventive aspects of the disease. This will be made possible under the plans for Health Cen-

ters already mentioned. We also have plans under way for coöperation with the Psychiatric Division in the study of the psychiatric factors involved. We feel that we need a little more time for each student, and that six weeks would be none too long for each fourth-year student to spend in our Service.

As a result of such a course as has been outlined the student would have a pretty thorough general medical training, so that even if the time thus spent should encroach upon that allowed to general medicine as such, the student would probably suffer no loss. For, with the training as I have conceived it, he could not do otherwise than come through it a better, well-rounded physician and also better prepared than is often the case at present, to meet many of the great social and economic problems so closely allied with the practice of medicine.

In general, the aim of our teaching is to provide first the material. This consists on the one hand of the patients specially selected because of their type of ailment, and on the other hand of the student, the material of which the physician is to be made. As to whether his selection is always as wise and as careful as might be, has been the subject of some question.

With this human material we provide the tools and the technique for the training of the student under expert guidance. He is also encouraged to learn to think for himself and thus to acquire wisdom rather than to accumulate knowledge. Having arrived at this point he may be a very well-trained man, but he is not yet a physician. That end is achieved only if and when the trained man with all his technique turns to the consideration of the original material, that is, the human individual under his care. When the proper contact between the individual patient and the individual student occurs, then is created the spark which transforms the technically trained student into that rare product, the true physician.

If, under the inspiration of proper leadership, this personal human interest can be widened to include the community environment surrounding the individual patient, then we may expect to obtain that still rarer flower of medical education,—the trained physician with social vision and broad human understanding.

THE INVOLVEMENT OF THE MYOCARDIUM IN TUBERCULOSIS[1,2]

A Review of the Literature and Report of 3 Cases

HENRY HORN AND OTTO SAPHIR

Tuberculosis of the myocardium is a rare disease. While an extension of the tuberculous process from the pericardium to the adjacent layers of the myocardium is often encountered in instances of tuberculous pericarditis, isolated myocardial tuberculosis is an unusual finding. In the following a review of the literature of tuberculosis of the myocardium is presented, and three additional cases are reported.

REVIEW OF THE LITERATURE

The rarity of myocardial tuberculosis

To Morgagni in 1761 is generally attributed the first published instance of myocardial tuberculosis, although Townsend mentions one previously reported in 1664 by Maurocordat, a Turkish physician. Not until 1806, forty-five years after Morgagni's observation, did the next case appear in the literature,—one of the nodular variety reported by Bayle. Laennec, writing in 1826, impressed with the rarity of the condition, assigned to it the thirteenth and last place in which tuberculosis could occur.

The number of published instances of tuberculosis of the myocardium increased somewhat after this period. In the English literature, the tumor-like auricular growth reported by Townsend in 1832 is the first recognized case. Haberling in 1865 presented the earliest review of this subject and listed 12 cases. In 1878 Saenger reviewed 19 instances and added three of his own, making the total twenty-two. Bollinger in 1890 spoke of myocardial tuberculosis as a rare disease. This investigator believed that muscle in general was very rarely the seat of tuberculosis, but that the myocardium was perhaps a bit more frequently involved than was striated skeletal muscle.

[1] From the Department of Pathology of the Nelson Morris Institute for Medical Research, Michael Reese Hospital, Chicago, Illinois.

[2] Aided by a grant from the Albert Kuppenheimer Fund.

In an extensive review of the literature in 1902 by Anders, the total of reported cases was brought up to seventy-two. From the time of Bollinger's report in 1890 and Raviart's study in 1906, it is interesting to note that 101 cases had been observed over a period of sixteen years, while only 79 cases had been recognized previously. Raviart listed 180 cases of which he believed 121 to be authentic.

The general incidence of tuberculosis of the heart may best be presented by a review of the statistical reports by various authors. Willigk, writing in 1856, found only two cases with myocardial involvement in 1,845 subjects with tuberculosis. Dittrich (1848) observed only one instance in 403 individuals with generalized tuberculosis. Klob, reviewing the protocols of Rokitansky between the years 1840–1860, met only one instance. Claessen stated that he had never encountered a case with tubercles in the myocardium. Saenger (1880) saw only 3 cases with myocardial involvement among 469 cases of tuberculosis. Valentine in 1894 could find myocardial lesions but seven times among 3,203 cases of generalized tuberculosis reported by various authors. Norris (1904), in a study of 1,764 hearts of tuberculous subjects, observed only 6 cases.

Pathological types of myocardial involvement

Tuberculosis of the heart may occur in one or more varieties. It is the opinion of some authors (Raviart, Gouley, Brehmer) that the disease may manifest itself as (1) a grossly nodular variety; (2) miliary type; (3) diffuse infiltrating form; (4) tuberculous myocarditis (interstitial and parenchymatous, including "sclerosis of the myocardium" (Raviart)).

These forms of tubercles occur either as a distinct type or may coexist with one of the other varieties. It is not uncommon, therefore, to find large solitary nodules in addition to small miliary tubercles in the same heart.

1. Nodular tubercles of the myocardium: The nodular variety has been seen most frequently. The nodules in the reported cases have varied markedly in size, from pea- to egg-size. In Townsend's case and that of Maurocordat the nodules in the auricle were so large as to obstruct the blood-flow in the pulmonary veins and to result in marked haemorrhage into the lungs. Reimer met with a similar case. Pollack encountered a large solitary nodule which occupied the interauricular septum in its entirety and extended to the base of the tricuspid valve. In Binder's case there was obstruction to auricular blood-flow by a large

tumor-like mass of the left auricle. In Eisenmenger's observation there was a large solitary tubercle, the size of a lemon, situated in the wall of the right auricle, with compresssion of the auricular lumen.

The nodules in instances of the nodular type of tuberculosis of the myocardium are usually rounded, yellowish-white, firm in consistency and sometimes present a caseous centre. Occasionally, however, a definite demarcation of the nodule is not present and the tubercle gradually merges into the adjacent parenchyma. They have been observed most often in the right heart and particularly in the wall of the right auricle. They vary in number from one to as many as eighteen (Fontoynont). In Adamson's case, the auricles were so markedly involved with multiple variously-sized masses "that it seemed they couldn't contract." They have been frequently well-circumscribed and sharply demarcated from the surrounding parenchyma. It is in these instances that they have offered some difficulty in their differentiation from gummata. As a matter of fact, the resemblance of tubercles to gummata is so striking that Virchow as late as 1865 denied the existence of tuberculous nodules of the myocardium, and stressed that syphilis was the cause of the nodular formations in the myocardium which were reported by various authors as tuberculosis.

Usually a pericarditis of varying degree has been associated with these gross nodules and miliary or larger tubercles in either the visceral or parietal components of the pericardial sac. Not infrequently the nodules project into the endocardium. It is remarkable when this occurs that the endocardial structure often remains intact. Raviart felt that this is possible only because of the absence of secondary infection, in contradistinction to the pronounced secondary infection which is present in instances of pulmonary tuberculosis. Nevertheless, ulceration of the endocardium and subsequent thrombus-formation have been seen and, in the cases reported by Hirschsprung, and by Sternberg, the erosion of the endocardium was the starting point of a generalized miliary tuberculosis with consequent death of the patients.

Histological sections present the usual picture of tuberculous granulation tissue. The surrounding myofibrils reveal evidence of atrophy, most likely the result of pressure.

2: Miliary tubercles of the myocardium: The miliary variety of the disease is decidedly less common than the gross nodular form, but is more frequently seen than the diffuse infiltrative type. Of 180 cases of

tuberculosis of the myocardium reviewed by Raviart in 1906, forty-one were classified as miliary tubercles. Since this survey 7 additional instances have been reported (Marshall, Carson, Brockhausen).

Much controversy has been waged over the comparative frequency of this lesion in subjects with generalized miliary tuberculosis. Weigert, Kaufmann, Maresch, and Leyden felt that miliary tubercles of the myocardium, and more particularly of the endocardium, were very frequently associated with generalized miliary tuberculosis. Leyden stated, for example, that they are seen in fully one-half of such cases, and Weigert felt that nine out of every ten cases of miliary tuberculosis show endocardial tubercles. A statistical review, however, casts doubt on such a conclusion. Reimer in 1876 found only 10 cases of miliary tuberculosis of the myocardium among 152 cases of generalized miliary tuberculosis. Simmonds in 1879, in a study of 125 cases of generalized miliary tuberculosis, did not find a single heart which contained miliary nodules. Schwerr, reviewing 123 instances of generalized miliary tuberculosis, found only one case. Boltz in 1890 found 11 instances of miliary tubercles in the myocardium among 176 cases of acute generalized miliary tuberculosis, and Reichenbach (1896) among 85 cases found but four examples. Haushalter in a study of 94 cases of generalized miliary tuberculosis encountered the lesion "only rarely." Ziegler, Waldeyer, and Orth were of the opinion that pure miliary tuberculosis of the myocardium was extremely rare. More recently, Gouley, Bellet and McMillan have remarked on its rarity.

There is no particular site of predilection, the myocardial miliary tubercles appearing in either auricle and either ventricle. The endocardial tubercles, however, according to Weigert, are most commonly seen in the right *conus arteriosus* (so-called "Weigert tubercle"); Ziegler also stated that tubercles are relatively more often encountered beneath the endocardium of the right ventricle.

The nodules are millet-seed sized, semitransparent, yellowish-gray or gray. They may be seen in the ridge of the coronary vessels immediately beneath the visceral pericardium, and not infrequently in the substance of the papillary muscles.

Microscopically the tubercles otten follow the course of the smaller blood-vessels (Klob) and are situated between the muscle fasciculi. In Brockhausen's case their proximity to the smaller blood-vessels was such as to cause a panarteritis with perivascular deposits not unlike Aschoff nodules. The typical histological characteristics of tuberculosis are, of course, present.

3: Diffuse infiltrative type: The third form of myocardial tuberculosis is the diffuse infiltrative type. This, according to Mönckeberg, is the specific diffuse productive tuberculous myocarditis, the least common of all the varieties of cardiac tuberculosis. This form is most frequently associated with pericarditis and most often the sequel to the latter.

Grossly the myocardium appears to be taken up by a uniformly gray to yellowish-gray firm material which infrequently appears to replace almost entirely the cardiac musculature in the involved portions.

The histological picture varies and often offers diagnostic difficulties. In Luescher's two cases, one presented a widespread distribution of granulation tissue associated with collections of lymphocytes, polymorphonuclear leucocytes, eosinophiles, giant cells of the Langhans type and giant cells which more closely resembled those of the foreign-body variety. The granulation tissue was so widespread that only an occasional island of muscle fibres and frequently only a single myofibril were noted. In the same heart typical miliary tubercles were also present. The second case revealed only a diffuse lymphocytic invasion associated with fatty infiltration of the myocardium. Most authors agree that the usual picture consists of granulation tissue with giant cells, endothelial cells and lymphocytes.

4: Chronic interstitial tuberculous myocarditis: The interstitial and parenchymatous myocarditis of Raviart has been a subject of some controversy. Brockhausen among others is of the opinion that this type is identical with the diffuse infiltrating form, and he therefore considers as tuberculous myocardial manifestations only the first three varieties. Pertik and Lancereaux similarly accept only the three forms of the disease. The so-called sclerosis of the myocardium supposedly due to tuberculosis was first described by Brehmer in 1883. This investigator reported an instance of fibrosis of the heart, with fibrous bundles parallel to muscular bundles and associated with tubercles. Histologically there was an increase in connective tissue and a moderate number of giant cells. There were no histiocytic cells or evidence of caseation. In 1903 Brucker reported another instance of myocardial fibrosis which was thought tuberculous in origin, the inference being that the scars represented healed tubercles.

It is extremely hazardous in the absence of a specific morphological picture to assign to a specific aetiological agent the blame for areas of fibrosis in the myocardium. Myocardial fibrosis might well be accounted

for by a previous diphtheria, rheumatic fever, scarlet fever, pneumonia, perhaps ischaemic alterations incident to disease of the coronary arteries, etc.

Liebermeister on the basis of his studies stated that, besides these forms, one may find as manifestations of tuberculous myocarditis interstitial alterations consisting mainly of cellular hyperplasia. The latter occur in the form of either linear or broader islands associated with hyperaemia and occasionally small haemorrhagic zones. The parenchyma in these areas usually presents only fatty metamorphosis. Giant cells and caseation are absent. There is occasionally a mesoarteritis and periarteritis. Gallavardin and Gravier reported similar changes in a heart which they attributed to tuberculosis, although "caseation, giant cells, nodular formation and tubercle bacilli were all wanting."

The other types of tuberculous myocarditis reported in the literature have also occasionally offered some difficulty in diagnosis. Of course, lesions consisting of typical tubercles with giant cells, endothelial cells, lymphocytes, and zones of necrosis are easy to interpret. Particularly in instances of large nodular solitary tubercles, and the so-called diffuse infiltrative varieties, have questions of diagnosis arisen. Attention has already been called to the resemblance of some forms of the nodular type to syphilitic gummata, not only at gross examination, but also in histological sections. All too frequently the Ziehl-Neelsen stain for tubercle bacilli has failed to reveal the presence of these organisms. Spirochaetal stains, too, have not aided materially in the diagnosis between tuberculous nodules and gummata. In many instances, therefore, authors have relied for ultimate diagnosis upon the concomitant findings in other viscera. Kirch, for example, believes that granulation tissue in the myocardium, if tuberculosis is present elsewhere, is sufficient evidence of tuberculosis of the myocardium. Massini and Luescher are of a similar opinion.

It may be mentioned in this connection that there exists a type of myocarditis described by Saltykow, and termed *specific productive myocarditis*. Von Gierke described the histological changes as characterized by a new growth of connective tissue with round cells, and much granulation tissue with many giant cells. Stains for acid-fast bacilli were negative. However, Saltykow believed in the tuberculous origin of these myocardial changes in spite of the absence of acid-fast organisms. Other authors (Busse and Hochheim, Berblinger, and Takata, etc.) hold syphilis responsible for these myocardial changes. Von Gierke, on the

other hand, stated that probably neither tuberculosis nor syphilis is the causative agent of the myocardial lesions, but that the aetiological moment is unknown and the myocarditis represents a disease *sui generis*.

In view of these rare cases of so-called specific productive myocarditis it must be emphasized that the presence of only granulation tissue with giant cells in the myocardium, in the absence of tuberculous lesions in other organs, does not signify a tuberculous origin of the myocarditis. Such cases should be classified as *productive myocarditis* or *granulomatous myocarditis*, etc., but should not be attributed to a tuberculous origin. The diagnosis, "tuberculous," should be made only if the histological changes in the myocardium are absolutely characteristic, or acid-fast bacilli are demonstrable, either by staining or by guinea-pig inoculation.

The reason for the relative rarity of myocardial tuberculosis offers an interesting topic for speculation. Some authors (Peter, Raviart) thought that the constant movement of the musculature is not conducive to the lodgment of tubercle bacilli or to the development of tubercles. Peter felt that the more active a function an organ has the less frequently it can be the seat of tuberculosis. Raviart suggested that the lactic acid produced by muscular activity offers the cardiac muscle a means of protection to Koch's bacillus. This explanation applies also to the rarity of tuberculosis of skeletal muscle.

Pathogenesis

In almost every instance, tuberculosis of the myocardium is secondary to a tuberculous focus elsewhere. There are, however, cases of so-called isolated primary tuberculosis of the myocardium, reported by Demme, Noel, Gunewardene, and more recently by Berger and Miller. The only manifestation of tuberculosis in these instances was found in the myocardium. However, as was mentioned before, it is very questionable whether or not some of these cases are tuberculous in origin. Luescher and Berger felt that in such there might be a particular type of organism which has selective affinity for cardiac muscle and to which the general body tissues are immune.

The mode of entrance to the myocardium may be (1) by direct extension, (2) by the lymphatic route, or (3) by the blood-stream. Very frequently, the myocardium is involved secondarily to a tuberculous pericarditis. Caseous tuberculous mediastinal lymph nodes, particularly the bronchial set, act often as a focus of infection for the pericardium and heart. This may occur, to be sure, by means of direct

contact or through lymphatic drainage. Since the drainage of the pericardium has been shown to be upward into the bronchial lymph nodes, the spread from these nodes to the pericardium necessitates a reversal of lymphatic flow. That this can occur has been amply demonstrated by von Recklinghausen.

That direct extension can and does occur is demonstrated rather strikingly in the nodular variety of tuberculosis of the myocardium. It is interesting to note that the wall of the right auricle is most frequently the seat of the nodular growths of tuberculosis and commonly the pericardium. When it is recalled that it is this portion which is more closely situated to the bronchial lymph nodes, it is reasonable to assume that mere contact is an important factor in the spread of the disease to the myocardium. It is conceivable, too, that direct extension through the pleura may occur.

The haematogenous route is the mode of infection of the myocardium in subjects with generalized miliary tuberculosis.

CASE REPORTS

During the past ten years there have been seen in this laboratory 140 cases of tuberculosis, of which thirty-four were of the generalized miliary type. Among the 34 cases of generalized miliary tuberculosis in which the myocardium was carefully examined histologically, we have encountered three instances of miliary tubercles in the myocardium. The latter were all found in subjects in the first decade of life.

1: Male, aged seven months. *Gross anatomical diagnosis:* Old tuberculous bronchopneumonia (right lower lobe). Chronic caseous tuberculosis of the tracheobronchial lymph nodes. Acute tuberculous bronchitis. Acute miliary tuberculosis of the lungs, liver and spleen. Acute tuberculous meningitis with moderate internal hydrocephalus. Passive hyperaemia of the liver and spleen (early).

Heart: No noteworthy gross changes. *Microscopic description:* There was an occasional roughly concentric group of cells easily distinguishable from the surrounding myocardium. Many of the cells presented an elongated vesicular nucleus. The cytoplasm was scanty and the cell borders irregular. The cells were apparently loosely connected to one another, and were frequently separated by small lymphocytes and by an indeterminate pale eosinophilic material. Situated toward the periphery of the nodule was a fair number of multinucleated cells of the Langhans type. The centre of this area appeared necrotic. A delicate network of fibrin was present throughout. The myofibrils adjacent

to the cellular zone were thin and atrophic in appearance. The Ziehl-Neelsen stain for tubercle bacilli was negative and concentration methods for demonstration of tubercle bacilli were also negative.

Fig. 1

Fig. 3

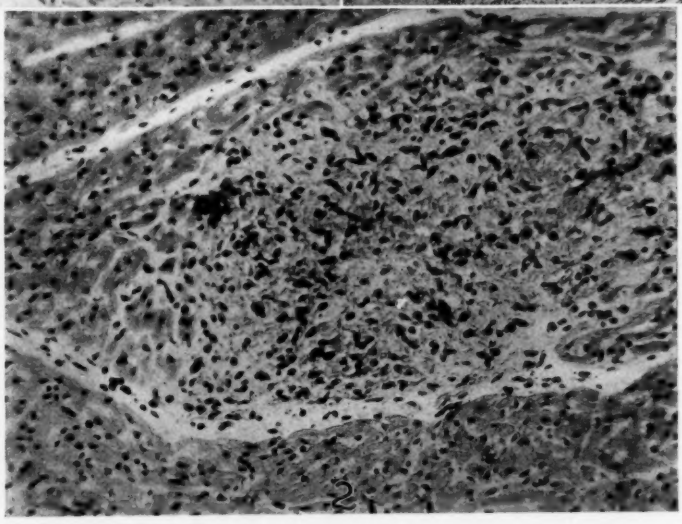

Fig. 2

Fig. 1. Miliary tubercle. Case 1 (haematoxylin-eosin preparation, × 90).
Fig. 2. Recent miliary tubercle. Case 2 (haematoxylin-eosin preparation, × 140).
Fig. 3. Conglomerate tubercle with much caseation. Case 3 (hematoxylin-eosin, × 50).

2: Male, three months old. *Gross anatomical diagnosis:* Tuberculous bronchopneumonia, left lower lobe. Chronic tuberculous lymphadenitis (tracheo-

bronchial and mesenteric lymph nodes). Acute miliary tuberculosis of the lungs, liver, spleen, kidneys, suprarenals, intestinal tract and heart. Acute tuberculous leptomeningitis.

Heart: The heart weighed 35 gm. There were a few widely scattered pearl-gray, millet-seed-sized nodules in the myocardium of the left ventricle. *Microscopic description:* The markings of the myofibrils were easily recognizable, and presented no notable histopathological alterations, except for the fasciculi close to the area to be described. Adjacent to the nodules seen in the gross, the fasciculi appeared compressed, thin and atrophic. Portions through the areas containing the pearly nodules revealed irregularly-shaped, granular and eosinophilic zones, surrounded by a narrow rim of lymphocytes, a few endothelial cells and plasma cells. An occasional multinucleated cell with peripherally disposed nuclei was also seen. Other portions of the myocardium presented roughly elliptical zones consisting of endothelial cells, and giant cells surrounded by lymphocytes. The basic structure of the myofibrils immediately adjacent to these irregular zones was not discernible; the fibrils often appeared interrupted. Ziehl-Neelsen staining revealed the presence of a few acid-fast bacilli morphologically typical of tubercle bacilli.

3: Female, aged ten years. *Gross anatomical diagnosis:* Old tuberculous bronchopneumonia, right lower lobe. Acute and chronic tuberculous lymphadenitis of the tracheobronchial lymph nodes. Acute miliary and conglomerate tuberculosis of both lungs. Intimal tubercles of pulmonary vein. Acute miliary tuberculosis of liver, spleen, kidneys, heart and brain. Tuberculous meningitis with moderate internal hydrocephalus.

Heart: Grossly the heart was normal in size, shape and position. There were no abnormalities encountered until the left auricle was examined. At the mouth of one of the right pulmonary veins was a polypoid projection which measured about 1 x 2 x 2 cm. in its greatest diameters and was subendocardial in origin. This was fairly firm and covered by intact endocardium. The nodule was pedunculated and, when cut, consisted of a central core of a cheesy-white material. On section, the structure of the pedicle was found to be similar to the main mass. *Microscopic description:* Sections of the left ventricular myocardium revealed an occasional roughly oval area consisting of a reticular and fibrin network supporting irregularly margined cells with elongated vesicular nuclei. Areas of necrosis and a few giant cells were also present. The centre of the large nodule seen in the left auricle was occupied by giant cells with peripherally placed nuclei and eosinophilic granular material. The periphery of the nodule showed many small lymphocytes and a few endothelial cells. The endocardium was intact. In other sections a vacuolization of the muscle fibrils was prominent. Sections through the wall of the pulmonary vein presented a typical intimal tubercle. The Ziehl-Neelsen

stain failed to reveal the presence of acid-fast organisms. Concentration method for demonstration of acid-fast bacilli was similarly negative.

COMMENT

The three cases are similar in many respects. There was a generalized miliary tuberculosis. In the heart only the myocardium was involved. In two instances the tubercles could be recognized with the naked eye, while in one case the diagnosis could be made only from the histological sections. Whereas the morphological changes were characteristic of tuberculosis, acid-fast organisms were found in only one instance.

In the first two instances, miliary tubercles were found in the myocardium. In the third a large conglomerate tubercle was seen, in addition to miliary tubercles. The conglomerate tubercle had involved the left auricle, while, according to the literature, the right auricle is more often involved than the left. As in other instances in the literature, the endocardium was not involved. Because of the intact endocardium, therefore, it is unlikely that the tubercle bacilli entered the myocardium through the endocardium. It is interesting that an intimal tubercle was also present in the pulmonary vein in this case.

It may be especially emphasized that among our 34 cases of generalized miliary tuberculosis, thirty occurred during the first decade of life and of these three revealed myocardial involvement. The greater part of miliary tubercles of the myocardium reported in the literature similarly were in subjects of the first decade. This might indicate that the finding of myocardial tubercles in the hearts of young subjects dying of miliary tuberculosis is attended with less difficulty because of the relatively larger area examined histologically. It seems conceivable that the comparative rarity of tubercles of the myocardium in adult hearts would be less marked if a greater number of microscopic preparations were made.

SUMMARY AND CONCLUSIONS

The literature of instances of tuberculosis of the myocardium is reviewed. Three main types can be differentiated, namely, the nodular, the miliary and the diffuse infiltrative types. The latter should be accepted only if either the histological changes undoubtedly are characteristic of tuberculosis or if the tubercle bacillus can be demonstrated either by guinea-pig inoculation or by staining methods. Otherwise, this form of tuberculosis cannot be differentiated from the so-called spe-

cific productive myocarditis (Saltykow, Gierke). For similar reasons it is difficult to attribute to a tuberculous origin, fibrous myocardial lesions which may be present in the hearts of subjects dying of tuberculosis. Hence, the term *chronic interstitial tuberculous myocarditis* should be discarded.

Three instances of miliary tuberculosis of the myocardium are reported, one of which also revealed a conglomerate tubercle. These three instances occurred in children. The literature also discloses that the greater percentage of miliary tubercles in the myocardium occurred in children. This may indicate that the finding of miliary tubercles in the hearts of young subjects dying of miliary tuberculosis is attended with less difficulty because of the relatively larger areas examined histologically.

BIBLIOGRAPHY

ADAMSON, W. W.: A case of tuberculosis of the myocardium, J. Path. & Bact., 1920, xxiii, 399.

ALBERT, H.: Ein Fall von Tuberkulose des Herzens, Inaug. Dissert., Kiel, 1883.

ANDERS, J. M.: Tuberculosis of the myocardium, Jour. Am. Med. Assoc., 1902, xxxix, 1081.

BAUMGARTNER, H.: Ueber spezifische diffuse productive Myocarditis, Frankfurt. Ztschr. Path., 1916, xviii, 91.

BAYLE, G. L.: Journ. de Med. par Corvisart, t. x, p. 45. (Cited by Albert.)

BEIFELD, A. F.: Tuberculosis of the myocardium: report of a case, Tr. Chicago Path. Soc., 1909, viii, 104.

BENVENUTI, E.: Il cuvre vei tuberculose e tuberculo del miocardio, Ref. Med., 1921. (Abstr. Zentralbl. Herz. & Gefässkr., 1921, xiii, 237.

BERBLINGER, W.: Diffuse gummoese myocarditis, Centralbl. allg. Path. & path. Anat., 1910, xxi, 1045.

BERGER, L., AND MILLER, J. C.: Ein Fall alleiniger Tuberkulose des Herzmuskels, Virchow's Arch. path. Anat., 1929, cclxxiii, 250.

BINDER, H.: Tumorartige Tuberkulose des Herzens, Zentralbl. Med., 1920, xli, 462.

BOLLINGER, O.: Ueber die Infectionswege des tuberkulösen Giftes, Muench. med. Wchnschr., 1890, xxxvii, 567.

BOLTZ, R.: Ein Beitrag zur Statistik und Anatomie der Tuberkulose im Kindesalter., Dissert., Kiel, 1890.

BREHMER, G.: Fibrosis of the myocardium, Inaug. Dissert., Halle, 1883.

BROCKHAUSEN, K.: Ein besonders gearteter Fall von Herzmuskeltuberkulose, Virchow's Arch. path. Anat., 1929, cclxxiv, 302.

BROSCH, A.: Herztuberkulose mit typischen Weilschen Symptomen-Complex, Wien. med. Presse, 1896, xxxvii, 985.

BRUCKER, T.: Vier Fälle von Tuberkulose des Myocards, Inaug. Dissert., Freiburg, 1903.

BUSSE, O., AND HOCHHEIM, W.: Ueber syphilitische Entzuendung der aeussern Augenmuskeln und des Herzens, Arch. Ophth., 1903, lv, 222.

CAPPER, A., AND STEWART, H. L.: Tuberculosis of the myocardium, Am. J. Dis. Child., 1932, xliv, 798.

CARSON, W. J.: Disseminated tuberculosis, M. J. & Rec., 1924, cxix, 281.
Tuberculosis of the Myocardium, M. J. & Rec., 1928, cxxvii, 610.

CLAESSEN, H.: Ueber Tuberkulose, kaesig-schwielige Mediastinopericarditis und Tuberkulose des Herzfleiches, Deutsch. med. Wchnschr., 1892, viii, 161.

DEMME, R.: Ein Fall von primärer Tuberkulose des Herzmuskels, Wien. med. Blätter, 1887, xlix, 1546. (Cited by Pollack.)

DITTRICH, F.: Prager Vierteljahrsch., 1848, ii, 141. (Cited by Norris.)

DUNHAM, E.: A case of solitary tubercle of the heart, Proc. New York Path. Soc., 1900–1901, clxix.

DURANTE, G.: Anatomie pathologique des Muscles in Cornil et Ranvier, Manual d'histologie pathologique, p. 357. (Cited by Raviart.)

EISENMENGER, V.: Zur Kenntnis der Tuberkulose des Herzmuskels, Ztschr. f. Heilk., 1900, xxi, 74.

FONTOYNONT, M.: Tuberculose du myocarde, Bull. Soc. Anat. Paris, 1897, xx, 101.

GALLAVARDIN, L., AND GRAVIER, L.: Myocardite interstitielle subaigue d'origine tuberculeuse, Arch. Mal. du Coeur, 1928, xxi, 472.

GAUCHER, E.: Tuberculose miliare du coeur et du pèricarde, des pleures, des poumons, etc., Bull. Soc. Anat. Paris, 1879, iv, 80. (Cited by Raviart.)

GENSERICH, V.: Grosser Solitärtuberkel im Myocardium und ein seltener Fall von gummöser, Erkrankung des Herzens mit exsudativer Pericarditis, Centralbl. allg. Path. & path. Anat., 1897, viii, 819.

GOULEY, B. A., BELLET, S., AND MCMILLAN, T. M.: Tuberculosis of the myocardium; report of 6 cases with observations on involvement of the coronary arteries, Arch. Int. Med., 1933, li, 244.

GROS, C.: Un coeur avec adhérence complète du pericarde et des granulations tuberculeuses qui paraissent développées dans le tissue cardiaque, Bull. Soc. Anat. Paris, 1859, xxxiv, 8. (Cited by Raviart.)

GUNEWARDENE, T. H., AND H. O.: Extensive primary tuberculous disease of the heart, Proc. Roy. Soc. Med., Child. Sect., 1919–1920, xiii, 38.

HABERLING: De tuberculose myocardii, Inaug. Dissert., Kiel, 1890–91. (Cited by Albert.)

HAND, A.: Tuberculosis of the myocardium, Arch. Pediat., 1898, xv, 184.

HAUSHALTER, P.: Ueber 94 Fälle von infantiler Tuberkulose mit Autopsie, Arch. f. Kinderhk., 1900, xxix, 45.

HAMANN, H.: Statistik der Tuberculose im Alter von 17–19 Jahren, Inaug. Dissert., Kiel, 1890–1891.

HIRSCHSPRUNG, H.: Grosser Herztuberkel bei einem Kinde, Jahrb. Kinderhk., 1882, xviii, 285. (Cited by Pollack.)

HLAVA: Tuberculose des Herzens, Wien. med. Wchnschr., 1901, li, 1228.

KACH, F.: Isolierte Herzmuskeltuberkulose, Muenchen. med. Wchnschr., 1917, lxiv, 1564.

KARSNER, H. T.: Human pathology, a textbook, J. B. Lippincott Co., Philadelphia & London, ed. 2, 1929.

KAUFMANN, E.: Beitrag zur Tuberkulose des Herzmuskels, Berl. klin. Wchnschr., 1897, xxxiv, 667.

KAUFMANN, E.: Lehrbuch der speziellen pathologischen-Anatomie, Berlin, W. de Gruyter, 1911, ed. 8, p. 52.

KIRCH, E.: Pathologie des Herzens, Ergebn. allg. Path. u. path. Anat., 1927, xxii, 1 & 206.

KLOB, J.: Zeitschr. k. k. Gesellsch. der Aerzte Wien., 1860, xlix, 218. (Cited by Pollack.)

LAENNEC, R. T. H.: Traite de l'auscultation mediate et des maladies des poumons et du coeur, 1826, ii, 31. (Cited by Anders.)

LANCEREAUX, E.: Traité d'anatomie pathologique, Paris, 1879, ii. (Cited by Mönckeberg.)

LEYDEN, E.: Ueber die Affectionen des Herzens mit Tuberkulose, Deutsch. med. Wchnschr., 1896, xxii, 1.

LIEBERMEISTER, G.: Studien über Komplikationen der Lungen-Tuberkulose und über die Verbreitung der Tuberkelbazillen in den Organen und im Blut der Phthisiker, Virchow's Arch. path. Anat., 1909, cxcvii, 332.

LUESCHER, W.: Ueber Myocarditis tuberkulosa, Schweiz. med. Wchnschr., 1921, li, 1158.

MARESCH, R.: Ueber Tuberkulose des Herzens, Wien. med. Wchnschr., 1920, lxx, 1873.

MARSHALL, H. T.: Endocarditis in tuberculosis, Bull. Johns Hopkins Hosp., 1905, xvi, 303.

MASSINI, R.: Ueber tuberkulose Myocarditis, Schweiz. med. Wchnschr., 1921, li, 1156.

MENDEZ, V.: Sobre tuberculosis del miocardio, Revista Soc. Med. Argentina, July, 1894. (Abstr., Zentralbl. Inn. Med., 1895, vi, 171.)

MÖNCKEBERG, J. G.: Die Erkrankungen des Myokards und des spezifischen Muskelsystemes, Handbuch der speziellen pathologischen Anatomie und Histologie, Henke-Lubarsch, Berlin, Julius Springer, 1924.

MORGAGNI: De sedibus et causis morborum, 1761, exp. 49, art. 4. (Cited by Albert.)

NOEL, J.: Gros tuberculose du coeur, Bull. Soc. Anat. Paris, 1892, lxvii, 403. (Cited by Raviart.)

NORRIS, G. W.: Tuberculosis and heart disease: based upon the study of 1764 autopsies, 1276 clinical histories, and a review of the literature, Am. J. M. Sc., 1904, cxxviii, 649.

ORTH, J.: A compend of diagnosis in pathological anatomy, New York, Hurd & Houghton, 1878.

PERTIK, O.: Pathologie der Tuberkulose, Ergebn. allg. Path. u. path. Anat., 1902, viii, 2 & 237.

PETER: Les maladies du coeur et la tuberculisation in leçons de clinique medicale, Paris, 1882, ed. 3, p. 194. (Cited by Raviart.)

POLLACK, S.: Ueber Tuberculose des Herzmuskels, Ztschr. klin. Med., 1892, xxi, 185.

PÜSCHMAN: Ein Beitrag zur pathologischen Anatomie der Herztuberkulose Leipzig, 1896, Rev. Centralbl. allg. Path. u. path. Anat., 1897, viii, 818.

RAVIART, G.: La tuberculose du myocarde, Arch. Méd. Exp. et d'Anat. Path., 1906, xviii, 141.

VON RECKLINGHAUSEN, F.: Tuberkel des Myocardium, Virchow's Arch. path. Anat., 1859, xvi, 172.

Ueber die venöse Embolie und den retrograden Transport in den Venen und in den Lymphgefässen, Ibid., 1885, c, 503.

REICHENBACH, A.: Ueber Tuberkulose des Herzens im Kindesalter sowie ueber ein tuberkeloseähnliches Knoetchen in der mitral Klappe, Inaug. Dissert., Zürich, 1896.

REIMER, M.: Casuistiche und pathologisch-anatomische Mittheilungen aus dem Nikolai-Kinder-Hospital zu St. Petersburg, Jahrb. Kinderhk., 1876, x, 219.

ROKITANSKY, C.: Miliare Tuberkulose des Herzfleisches, Ztschr. k. k. Geselsch. Aerzte Wien., 1860. (Cited by Albert.)

SAENGER, M.: Ueber Tuberkulose des Herzmuskels, Arch. Kinderhk., 1878, xix, 448.

SALTYKOW, S.: Spezifische productive Myocarditis, Verhandl. deutsch. path. Gesellsch., 1914, xvii, 321.

SANGALLI, G.: Gatti straordinari di somma estensione della tuberculosi nel miocardio dell'uomo, Gaz. Med. Comb. Milano, 1896, xlii, 411. (Cited by Raviart.)

SAPHIR, O.: Syphilitic myocarditis, Arch. Path., 1932, xiii, 226 & 436.

SCHWERR, W.: Ein Beitrag zur Statistik und Anatomie der Tuberkulose im Kindesalter, Inaug. Dissert., Kiel, 1884.

SIMMONDS, M.: Ein Beitrag zur Statistik und Anat. der Tuberkulose im Kindesalter, Inaug. Dissert., Kiel, 1879. (Cited by Albert.)

STARK, J. R.: Acute tuberculous parietal endocarditis, J. Lab. & Clin. Med., 1916–1917, ii, 731.

STERNBERG, K.: Conglomerat Tuberkel des rechten Vorhofes, Wien. med. Wchnschr., 1902, lii, 623.

TAKATA, F.: Beitraege zur Pathologie der syphilitischen Myokarditiden, Virchow's Arch. path. Anat., 1920, ccxxviii, 426.

TOWNSEND, R.: Death from asphyxia caused by large tuberculous masses, developed in the parieties of the left auricle compressing the trunks of the pulmonary veins, Dublin J. Med. Soc., 1832, i, 176.

THOMPSON, J. G.: An unusual case of diffuse tuberculous infiltration of the myocardium, J. Path. & Bact., 1930, xxxiii, 259.

VON GIERKE, E.: Ueber granulierende produktive Myokarditis mit Regeneration von Herzmuskelfasern, Beitr. path. Anat. u. allgem. Path., 1921, lxix, 72.

VALENTINE, G.: Contribution à l'étude de la tuberculose myocardique, Thèse de Paris, 1894, (46). (Cited by Anders.)

VIRCHOW, R.: Die krankhaften Geschwülste, Berlin, 1864–1865, ii, 442.

WALDEYER, W.: Tuberkulose des Myocardiums und des Gehirns, Virchow's Arch. path. Anat., 1866, xxxv, 218.

WEBER, C.: Ein Fall von miliär Tuberkulose des Endocards, Inaug. Dissert., Freiburg, 1889.

WEIGERT, C.: Zur Lehre von der Tuberkulose und von verwandten Erkrankungen: Miliartuberkulose des Herzens, Virchow's Arch. path. Anat., 1879, lxxvii, 293.

WEISS, E.: Tuberculosis of the heart, Arch. Int. Med., 1922, xxix, 64.

WILLIGK, G. A.: Sectionsergebnisse d. Prager. anat. Anstalt: Vierteljahresschrift für die praktische Heilkunde, Prag., 1854, xliv, 86. (Cited by Pollack.)

ZIEGLER, E.: Lehrbuch allgem u. speciel. Pathol. u. patholog. Anat., g. Fischer, Jena, 1892.

JUVENILE DIABETES AND TUBERCULOSIS[1]

A. L. NEWCOMB

The importance of an intensive study of each diabetic patient for incipient tuberculosis has been emphasized recently by Root (1) in four admirable papers. He states that very few early cases have been reported in the literature and that only ten of their 245 tuberculous diabetics were discovered in an early stage of the disease. Therefore, it seemed imperative to us that each diabetic child in the clinic should have a tuberculin skin test (if one had not been performed), a thorough scrutiny of the family history for exposure to tuberculosis, and a roentgenogram of the lungs if the skin tests were positive.

Since Root has stated that the incidence of adult-type tuberculosis in diabetic children in Massachusetts is thirteen times that in the general school-group of similar ages, it seemed advisable to retest the negative reactors once a year and to reëxamine the lungs of the positive reactors roentgenologically every six to twelve months in an effort to detect the early onset of tuberculosis. Recently, Kennedy (2) failed to find any cases of phthisis developing before the age of twenty years in a smaller series.

METHOD

A Pirquet scarification test was first performed on the forearm and, if found negative, was followed by a Mantoux intracutaneous test, 1:1000. Tests were read at the end of 48 to 72 hours in all instances. Roentgenograms of the lungs were taken of all positive cases.

In our 40 cases of diabetes there were six whose skins reacted positively to the tuberculin. Two patients had had diabetes for less than six months when the test was made, one for $3\frac{1}{2}$ years, two for over $4\frac{1}{2}$ years, and one for over $6\frac{1}{2}$ years. It is interesting to compare the incidence of positive skin tests among our diabetic children with similar series of Vienna and Boston, as follows:

[1] From the Children's Memorial Hospital and the Northwestern University Medical School, Chicago, Illinois.

age in years	Root		Priesel & Wagner		Author	
	total cases	tuberculin-positive	total cases	tuberculin-positive	total cases	tuberculin-positive
1–5.....	16	5	10	0	8	0
6–10.....	36	15	28	7	19	1
11–15.....	38	23	37	22	13	5
Total.....	90	43	75	29	40	6
Percentage..		47.7		38.6		15.0

Infection in the 11- to 15-year group is very much less than in Boston and Vienna, is surprisingly low in the 6- to 10-year group, and is absent in the children under the age of six years.

The difference in the percentages could be interpreted in the following manner: Our series is smaller in total numbers and in relative numbers in the 11- to 15-year group, in which more infection is ordinarily expected. Further, it is well recognized that the incidence of tuberculous infection varies greatly with the community. Chadwick and Zacks (3), using Pirquet tests, showed an incidence of infection in Massachusetts of from 21 to 35 per cent in the 5- to 15-year group, respectively, in over 42,000 children, while Dickey and Seitz (4), using intracutaneous tests, reported only 6.8 per cent positive among 3,600 fourteen-year-old children in San Francisco. Webb (5) found a 14.5 per cent incidence of infection in Chicago children up to 15 years of age, and recently Drolet (6) reported a 19 per cent incidence of infection in New York City in the group under 15 years. Both of the latter investigators used the intracutaneous method.

Root (1) noted the presence of coma five times as frequently among the tuberculous as among the nontuberculous diabetics, but failed to find any increase in the severity of the diabetes as determined by insulin dosage when compared with similar nontuberculous patients. Ketosis requiring hospitalization occurred 18 times in 6 infected children (one child, *S. Z.*, was readmitted nine times) and 25 times in 12 noninfected cases of similar age-groups. The following case histories are presented to show the number of attacks of acidosis, the possible effects on the glucose tolerance, and the X-ray findings:

W. H., a boy with onset of diabetes at $6\frac{3}{4}$ years, who had frequent antrum infections and local infections of the fingers, was readmitted three times in five years for acidosis. Tolerance for glucose was 103 gm. in 1929 (7), 136 in 1933, and for 1934 has fallen to 118 "G." Mantoux test negative after $1\frac{3}{4}$ years of the disease, but became positive after $4\frac{5}{6}$ years. No history of exposure to tuberculosis. Roentgenological report by Dr. W. E. Anspach in April, 1934, negative for pulmonary disease or calcification.

J. D., a boy with onset of diabetes at 8½ years, readmitted to Hospital twice, once for rather severe acidosis due to unrestricted diet, and a second time for tonsillectomy complicated by scarlet fever and followed by pneumonia and empyema in 1930. Mantoux test positive in 1934 after 4½ years of the disease. One sister has a chronic cough. X-ray revealed "a small cluster of unusually fine densities superimposed on the fifth rib near the left costal margin. Unable to state that this is a definite calcification. There is a slightly prominent left hilum shadow which could be due to enlarged glands, but this has been present on all the films following the previous empyema and would not necessarily be due to a tuberculosis." Glucose tolerance 128 gm. "G" in 1930, 148 gm. in 1931 and 1932, and 156 in 1933.

D. B., a girl, whose diabetic symptoms began at 12⅛ years, had a tolerance for 120 gm. "G" for first three months of observation and then developed persistent upper respiratory infection with permanent depression of tolerance to 90 gm. Died four months later of diabetic coma. Mantoux test, 1:100, slightly positive during upper respiratory infection. While no previous tuberculin test was made, it seems possible that this infection may have been the primary tuberculous infection. No X-ray of the lungs made.

L. S., a girl with onset of diabetes at 10¾ years, had a tolerance for 158 gm. "G" for first four months of the disease. After an episode similar to that in the preceding case, her tolerance fell to 62 gm. Readmitted twice to the Hospital. Pirquet positive on first admission. X-ray revealed "a small calcified area just above the right diaphragm at level of the fifth cartilage. Larger irregular area of calcification in left hilum seen through the heart shadow. Diagnosis: Healed primary complex of left lung field." Patient moved to California in February, 1931, six months after the X-ray examination.

S. Z., a boy with onset of symptoms of diabetes at 5¼ years, had negative Pirquet one year after onset, but positive Mantoux after 2¾ years of the disease. X-ray showed "prominent right hilum shadows and the lateral margins of the mediastinum fade into the lung tissue. Unable to rule out enlarged glands producing the above described shadows. No evidence of intra-pulmonary calcification." This patient readmitted to the Hospital eight times with various respiratory complaints and ketosis and once for acute gangrenous appendicitis. Management of the disease was never satisfactory, although clinic attendance was very good. A definite history of exposure to tuberculosis from the landlady was found. Tolerance never rose above 60 "G" the first year of the disease, was 54 during 1932, and rose to 120 during 1933 and 1934.

V. P., an Italian boy with onset of diabetes at five years, readmitted twice during the 4½ years that he was under observation. The diabetes was complicated by bilateral cataracts and progressive nerve deafness. Tolerance for glucose was 106 gm. "G" in 1930, 140 in December, 1932 and 120 in 1934. Pirquet negative after five years of the disease, but became positive two years later. No X-ray findings of pulmonary tuberculosis.

COMMENT

Of 6 cases of juvenile diabetes mellitus which reacted positively to the tuberculin test, definite calcification was found in the lungs of one child and a questionable deposit of calcium was described in another child's chest X-ray. The latter child and one other showed large hilar lymph nodes. Two roentgenograms were reported free from any pulmonary disease. No evidence of phthsis has been found in any of the chest X-rays up to the present.

SUMMARY

1. Six, or 15 per cent, of 40 diabetic children from 1 to 15 years old reacted positively to intracutaneous tuberculin skin tests in contrast to 38.6 per cent in Vienna and 47.7 per cent in Boston.

2. No case of adult-type tuberculosis or phthsis was found.

REFERENCES

(1) Root, H. F.: New England J. Med., 1934, ccx, 1, 78, 127, 192.
(2) Kennedy, W. R.: Canadian Med. Jour., 1933, xxix, 482.
(3) Chadwick, H. D., and Zacks, D.: Amer. Rev. Tuberc., 1930, xxii, 626.
(4) Dickey, L. B., and Seitz, R. P.: Ibid., 1931, xxiii, 13.
(5) Webb, C. H.: Ibid., 1932, xxvi, 583.
(6) Drolet, G. J.: Ibid., 1934, xxx, i.
(7) Newcomb, A. L.: Jour. Ped., 1934, iv, 617.

Addendum: Since this paper was submitted for publication, practically all of the children were retested with intracutaneous tuberculin test. No new positive reactors were discovered.

However, among the 10 new cases admitted to the clinic, all of whom had a negative skin test on initial admission, two have since become positive. A boy, *R. L.*, was faintly positive to 1:1000 dilution, and definitely positive to 1:100. X-ray films of his chest were entirely negative. *E. P.*, a boy, was negative to 1:1000 dilution in March of 1935, and became violently positive in July, 1935. X-ray revealed a fairly wide area of increased density about both hila. The patient's skin became a darker yellow to orange, and the glycosuria was more difficult to control. The patient's mother had an active pulmonary tuberculosis. Three older children in this family had positive skin tests.

age in years	*total cases*	*tuberculin-positive*
1–5	11	0
6–10	25	3
11–15	14	5
	50	8

ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF LOBAR PNEUMONIA[1]

THOMAS KLEIN AND VERNON LEE TUCK

Therapeutic pneumothorax in the treatment of lobar pneumonia was first used by Friedman (1) in 1921. At that time he reported 7 cases, all of whom recovered without complications. The same year David (2) reported an additional series of 6 cases with complete recovery. The outstanding features reported were a relief of pain in the affected side, with improvement of the respiratory rate and the general clinical picture. Two years later Schottky (3) reported a single case with recovery. No further attention was called to this therapeutic measure until 1928, when a group of pediatricians, Ibraham and Duken (4), Jahr and Neumann (5), and Klotz, reported 17 cases in children with 3 deaths. They advised against this form of treatment mainly because most children recover from this type of pneumonia with more conservative treatment. Taylor (6), in 1931, used therapeutic pneumothorax in the treatment of pleurisy in pneumonia in 3 cases with complete relief of pain. In 1932 Coghlan (7) reported 6 cases with one death, a fatality which he attributed to an error in judgment in a very critical patient. He injected 750 cc. of air which was followed immediately by a crisis,—marked cyanosis, excessive sweating, and signs of right heart-failure. Since that time other cases have been reported by Hanau (8), Guadarrama (9), Li (10), Perlroth and Topercer (11), and Anderson (12), all of whom commented favorably upon the procedure. At the Philadelphia General Hospital during the years 1930–1932 six sporadic cases were treated with gratifying results.

However, it was not until the experimental work of Lieberman and Leopold (13) at the University of Pennsylvania that the work has been placed upon a definite experimental and scientific basis. They treated 18 dogs with unilateral pneumonia, with only three deaths. All dogs were treated on the second day of the disease, with a refill the following day. At the same time, they used 18 control dogs, of which 13 died and

[1] Read at the annual meeting of the American Clinical and Climatological Association, Toronto, Ontario, May, 1934.

TABLE 1

NAME	AGE	SEX	COLOR	DURATION OF DISEASE PRIOR TO ADMISSION	DATE OF ILLNESS	TYPE OF SPUTUM	BLOOD CULTURE	WASSERMANN	AREA INVOLVED	THERAPEUTIC PNEUMOTHORAX		RESULT	TEMPERATURE	COMPLICATIONS
										Date	Amount			
									lobe		*cc.*			
J. T.	45	M	B	2 weeks	2–23–34	Pneum. 4	Pneum. 4 and Strep. haem.	4+	Right lower	3– 9–34	300	Recovery	Lysis	None
P. K.	30	M	W	2 days	1– 9–34	Not taken	Neg.	0	Right lower	1–11–34 1–12–34	300 400	Recovery	Crisis	None
J. B.	47	M	B	3 days	1–15–34	Pneum. 4	Neg.	4+	Left upper	1–19–34 1–20–34	400 500	Recovery	Crisis	None
B. G.	63	M	B	4 days	1–18–34	Pneum. 1	Pneum. 4	0	Right upper	1–23–34 1–24–34	400 500	Recovery	Crisis	Pericarditis
G. F.	55	M	W	2 days	1–27–34	Not taken	Not taken	0	Right upper	1–29–34 1–30–34	450 500	Death, 2–2–34	Crisis	Toxic psychosis: Schilling count pointed to bacteraemia
G. S.	48	M	B	1 day	2– 6–34	Not taken	Not taken	0	Right upper	2– 7–34 2–10–34	400 500	Death, 2–14–34	Lysis	Toxic psychosis: afebrile for 5 days prior to death
S. L.	40	M	B	4 days	2– 8–34	Pneum. 4	Neg.	Kahn pos.	Left upper	2–13–34	100	Recovery	Lysis	None
D. S.	32	M	W	4 days	2–10–34	Pneum. 1	Neg.	0	Left lower	2–15–34 2–16–34	400 500	Recovery	Crisis	None
C. S.	45	M	W	2 days	2–20–34	Not taken	Not taken	0	Left lower	2–23–34 2–24–34	425 150	Death, 2–25–34	Crisis	Overwhelming infection
J. H.	32	M	W	4 days	2–20–34	Pneum. 2	Not taken	0	Left lower	2–25–34 2–27–34	425 500	Recovery	Lysis	Pericarditis

P. C.	?	M	W	4 days	2–24–34	Not taken	Not taken	0	Right upper	2–28–34	425	Death, 2–28–34		Died 2 hours after pneumothorax
W. R.	36	M	B	6 days	2–20–34	Not taken	Pneum. 1	0	Right lower	3– 3–34	200	Death, 3–4–34		Died 19 hours after pneumothorax: moribund at time: done to relieve pain only
T. P.	49	M	B	2 weeks	2–28–34	Pneum. 4	Pneum. 4 (25 colonies)	0	Entire right lung	3–14–34 3–15–34	350 300	Death, 3–23–34	Crisis	Acute endocarditis: *Streptococcus haemolyticus*
J. S.	45	M	B	2 days	3–12–34	Pneum. 1	Neg.	4+	Right lower	3–15–34 3–16–34 3–17–34 Pos. pressure at that time	450 450 100	Death, 3–25–34	Lysis	Death due to toxic myocarditis
E. W.	29	F	W	2 days	3–16–34	Pneum. 1	Neg.	0	Left lower	3–17–34	100	Recovery	Lysis	Had lung abscess following tonsillectomy 11 years prior to pneumonia: had positive intrapleural pressure after 100 cc.
H. C.	26	M	B	1 day	1–31–34	Not taken	Not taken	0	Right upper	2– 1–34	500	Death, 2–1–34		Died 2 hours after pneumothorax
V. A.	21	M	W	1 day	12–28–33	Not taken	Not taken	0	Left lower	12–31–33 1– 1–34	150 50	Recovery	Lysis	None
B. S.	15	M	W	4 days	12– 7–33	Not taken	Not taken	0	Left lower	12–11–33 12–12–33	400 500	Recovery	Lysis	None
L. C.	45	M	W	4 days	3– 7–34	Pneum. 4	Neg.	0	Left lower	3–21–34 3–23–34	450 450	Recovery	Crisis	None
M. R.	48	F	W	In hospital	4– 6–34	Not taken	Not taken	0	Entire right lung	4– 7–34 4– 8–34	300 400	Death, 4–10–34	Lysis	Auricular fibrillation
J. H.	50	M	W	4 days	4– 3–34	Not taken	Not taken	0	Entire upper & middle	4– 8–34	450	Death, 4–8–34		Died 5 hours after pneumothorax

TABLE 1—*Continued*

NAME	AGE	SEX	COLOR	DURATION OF DISEASE PRIOR TO ADMISSION	DATE OF ILLNESS	TYPE OF SPUTUM	BLOOD CULTURE	WASSERMANN	AREA INVOLVED	THERAPEUTIC PNEUMOTHORAX		RESULT	TEMPERATURE	COMPLICATIONS
										Date	Amount			
									lobe		*cc.*			
J. W.	38	M	B	2 days	12–24–33	Not taken	Pneum. 4	0	Right lower	12–26–33 12–27–33	500 450	Death, 12–27–33	Crisis: temperature came down to normal after each pneumothorax	Autopsy record: confluent bronchial pneumonia; acute pleuritis with fibrinous adhesions
H. W.	42	M	W	1 day	2–18–34	Pneum. (no type)	Neg.	0	Right middle & lower	2–21–34 2–22–34 2–23–34 2–24–34	350 450 150 25	Recovery	Lysis	None
M. S.	29	F	B	1 day	12–30–33	Friedländer's bac.	Neg.	0	Right upper	12–31–33 1– 1–34	350 400	Recovery	Crisis	None
M. R.	44	F	B	1 day	12–26–33	Pneum. 1	Neg.	0	Right middle	12–27–33 12–28–33 12–29–33	50 400 300	Recovery	Lysis	None
L. E.	30	F	B	5 days	12–10–33	Pneum. 4	Neg.	0	Left upper	12–16–34	400	Recovery	Crisis	None
C. G.	41	M	B	1 day	6–14–33	Pneum. 4	Not taken	0	Right lower	6–15–33 6–17–33	330 250	Recovery	Crisis	None
S. N.	54	M	B	4 days	12–15–33	Pneum. 4	Not taken	0	Right upper	12–19–33 12–20–33	500 500	Death, 12–23–33	Lysis	Pneumococcic meningitis: first meningeal symptoms, 12–21–33
E. W.	55	M	B	1 day	11–27–33	Pneum. 4	Not taken	3+	Right lower	11–29–33	250	Recovery	Crisis	Aortic aneurysm
M. S.	53	M	W	4 days	5– 1–34	Pneum. 2	Neg.	Not taken	Right middle	5– 2–34 5– 3–34	600 600	Recovery	Lysis	None
C. McC.	19	M	W			Pneum. 4	Neg.	Not taken	Right upper	4– 9–34	300	Recovery	Lysis	None

T. W.	48	M	B	3 days	4–22–34	Pneum. 4	Pneum. 4	Not taken	Right lower	4–23–34 4–24–34	600 400	Death, 4–28–34	No change in temperature	None
G. S.	13	F	B	1 day	4–16–34	Pneum. 4	Neg.	Not taken	Right upper	4–19–34	425	Recovery	Crisis	None
J. M.	58	M	B	4 days	4–12–34	Pneum. 2	Neg.	Not taken	Right lower	4–12–34 4–13–34	500 600	Death, 4–15–34	No temperature effect	Toxic psychosis
K. M.	54	F	W	3 days	4– 4–34	Not taken	Not taken	Not taken	Left lower	4– 4–34 4– 6–34	475 400	Recovery	Crisis	None
C. C.	30	M	W	2 days	3–29–34	Pneum. 4	Neg.	0	Right lower	3–30–34 4– 2–34	500 500	Recovery	Lysis	None
R. T.	45	M	B	Unknown	3–28–34	Pneum. 4	Neg.	0	Right upper	3–28–34 3–29–34	450 450	Recovery	Crisis	Jaundice
C. T.	69	M	B	Unknown	3– 3–34	Pneum. 4	Neg.	0	Right middle	3– 3–34	450	Recovery	Crisis	Toxic psychosis: complete recovery in 6 weeks
J. C.	46	M	W	Unknown	2–16–34	Pneum. 1	Neg.	4+	Left lower	2–16–34 2–17–34	400 400	Recovery	Lysis	Empyema: thoracotomy
R. G.	23	M	B	1 day	3–12–34	Pneum. 1	Pneum.	4+	Left lower	3–13–34 3–14–34	350 450	Recovery	Lysis	Developed fluid: did have thoracotomy: haemolytic strep. in fluid: found in only one tap
L. H.	34	M	B	3 days	3–13–34	Pneum. 2	Neg.	2+	Right lower; later developed left upper	3–14–34 3–15–34	500 250	Recovery	Crisis	Alcoholic delirium
R. H.	25	M	B	2 days	3–19–34	Pneum. 2	Neg.	0	Right lower	3–19–34 3–20–34 3–22–34	650 700 500	Recovery	Crisis	None
J. M.	33	M	B	2 days	3–24–34	Pneum. 4	Pneum.	0	Right lower	3–25–34	450	Recovery	Lysis	After air-injection developed a slow spontaneous pneumothorax with marked mediastinal shift: later empyema followed thoracotomy

5 recovered. With the stimulus of this work we endeavored at the Philadelphia General Hospital to study further the clinical value of artificial pneumothorax in unilateral pneumonias, and are reporting a series of 43 cases. This is done solely to enlarge the number of reported cases in order to help evaluate at a later date the real clinical value of the procedure.

The rationale of the procedure is primarily twofold. First, by separating the inflamed visceral and parietal layers of the pleura we relieve instantly the pleural pain. This allows for a slowing of the respiratory rate with deeper inspiration and better ventilation by the unaffected lung. Consequently, cyanosis will diminish to a great extent, or wholly disappear. The air injected is apparently absorbed rapidly and unless a refill is done within twenty-four hours the pain with increased respiratory rate will reappear. Many patients will ask for a refill when this occurs. Second, it has been definitely shown at autopsy, and roentgenographically, that the affected portion of the lung is compressed; and thus the blood-flow in the affected lung is cut down. Lymph-stasis, with a diminution of absorption of toxins, must also play a similar rôle in helping reduce the toxaemia from which all pueumonic patients suffer. In turn, there is in many cases a rapid fall in temperature and pulse-rate, with an increase in the sense of well-being. The blood-pressure does not show any marked variation as compared before and soon after the air-injection. The leucocyte count falls rapidly after the fall in temperature and is most marked in that group of patients in whom a crisis is precipitated. In addition to a definite decrease in mortality, the procedure shortens, in the vast majority of cases, the febrile period, and markedly diminishes the days of hospitalization.

In our series of 43 cases, there was an alleviation of the pleural pain in all of the cases treated. This was followed invariably by a diminution in cyanosis and a slowing of the respiratory and pulse-rates. A definite crisis occurred in 19 cases within forty-eight hours after the initiation of pneumothorax therapy. In 18 cases the temperature came down by lysis. Four cases, all of whom were moribund at the time of air-injection, died from two to nineteen hours after the initial treatment, and the temperature-curve was not affected. In the patient who lived nineteen hours the procedure was done solely for the relief of pain, inasmuch as it was uncontrollable by opiates. The other 3 patients died from two to five hours after the initial air-injection. In the remaining 2 cases, the temperature-curve was not affected, even though both

patients had two injections of air, 600 cc. and 400 cc., and 500 cc. and 600 cc., respectively, within a period of twenty-four hours. One of the patients died at the end of twenty-four hours and the other in three days.

The age of the patients varied from 13 to 69 years. There were 6 females and 37 males, and 24 colored and 19 white patients. Eight of the cases had positive blood cultures. By sputum-typing, the cases were divided into the following groups: seven of type 1; five of type 2; none of type 3; fifteen of type 4; and one of Friedländer's bacillus. The remaining cases were not typed.

The time of the first injection varied from one to six days after the onset of the pneumonia. In the majority of the cases the collapse therapy was started on the second and third days. Our best results were obtained in the cases injected early.

The group of complications was rather widespread and interesting. A large percentage will show a small collection of fluid roentgenographically, and a lesser group by physical findings. Most of the fluids remain sterile and do not necessitate tapping or drainage. Two of this group developed empyema with subsequent thoracotomy. One patient, after his first injection of 450 cc. of air which was done without any difficulty whatsoever, developed a complete spontaneous pneumothorax with marked mediastinal and cardiac shift. This apparently came on very slowly and did not occasion any discomfort for the first twenty-four hours. At that time, when introducing the needle, we found a positive manometer reading. Within another forty-eight hours it was necessary to aspirate some of the air to relieve mediastinal pain and dyspnoea. The patient later had a purulent fluid which necessitated thoracotomy. After evacuation of the pus, the roentgenogram showed a marked collapse of the entire lung which was adherent to the central portion of the diaphragm. At this date he is still in the hospital and doing nicely. Atmospheric pressure is undoubtedly a factor in his present collapse, and not until his thoracotomy wound is healed do we expect to get an expansion of the lung. The other empyema case also recovered.

Two patients, both of whom recovered, had acute pericarditis as a complication. One had a pneumococcic meningitis which developed on the sixth day of disease and twenty-four hours after his second and last collapse. Out of 4 cases that developed a toxic psychosis, three died. The other recovered at the end of six weeks, and was discharged from our psychopathic department. Another case was complicated by an

alcoholic psychosis, with recovery. At autopsy one case showed an acute haemolytic streptococcic endocarditis. Only one case showed a marked jaundice.

Mortality: In the pneumonia wards during the interval in which these cases were treated, there were 243 cases in all. Two hundred of these were treated by other forms of therapy, such as routine symptomatic, foreign protein, and dehydration measures. Serum therapy was not used, owing to its cost. Of this group, 83, or 41.5 per cent, died. Thirty per cent of this group had postitive blood cultures, with a mortality of 77 per cent. In the pneumothorax group, none of which was especially selected, and, if the case was seen late, and doing well, was not given this form of therapy, a mortality of 14 deaths, or 32.6 per cent, occurred. If the 4 cases that were moribund at the time of their collapse, and in which only one injection was given, be excluded, the mortality would be 25.6 per cent. This we believe to be the more sensible classification. Of the 8 positive blood-culture cases, 4, or 50 per cent recovered.

CONCLUSIONS

1. Pneumothorax therapy in unilateral lobar pneumonia is of definite value in the relief of pleural pain. It also diminishes to a great extent the accompanying cyanosis and toxaemia.

2. An early crisis is precipitated in a large proportion of the cases (44.2 per cent in this group).

3. The mortality in this group, as compared to other forms of therapy excluding serum therapy, was distinctly less (25.6 per cent as against 41.5 per cent.).

4. We feel that further studies should be made upon a larger series of cases to evaluate eventually a correct interpretation of this form of therapy.

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REFERENCES

(1) Friedman, U.: Deutsch. med. Wchnschr., 1921, xlvii, 443.
(2) David, O.: Ibid., p. 802.
(3) Schottky, P.: Med. Klin., 1923, xix, 1298.
(4) Ibraham, J., and Duken, J.: Arch. f. Kinderhk., 1928, lxxxiv, 241.
Duken, J.: Klin. Wchnschr., 1930, ii, 2195.

(5) JAHR, J., AND NEUMANN, R.: Ibid., p. 2200.
(6) TAYLOR, A. B.: Practitioner, 1931, cxxvii, 389.
(7) COGHLAN, J. J.: Lancet, 1932, ii, 13.
(8) HANAU, G.: Gasz. Osp. Milane, 1932, liii, 257.
(9) GUADARRAMA, L.: Medicina Mexico, 1932, xii, 141.
(10) LI, K. H.: Chinese Med. J., 1932, xlvi, 886.
(11) PERLROTH, S., AND TOPERCER, M.: Wien. klin. Wchnschr., 1932, xlv, 1508.
(12) ANDERSON, H. G.: Ibid., p. 769.
(13) LIEBERMAN, L. M., AND LEOPOLD, S. S.: Am. J. M. Sc., March, 1934, p. 315.

INTRAPLEURAL PRESSURE IN ARTIFICIAL PNEUMOTHORAX

A Statistical Study of the Range of Intrapleural Tension in 601 Tuberculosis Patients[1]

EMIL BUNTA

INTRODUCTION

A search of medical references has failed to disclose any previous work on the clinical range of intrapleural pressure in artificial-pneumothorax patients. Available reports on intrapleural pressure embodied data based on average figures, a method which does not account for normal variations from the average, nor describe the normal and abnormal range. Clinical and experimental observations have substantiated the fact that intrapleural tension is not a fixed factor, but that it, at any moment, is the resultant of variable forces which enter into its production. It is generally known, furthermore, that individual measurements of intrapleural pressure always deviate, more or less, from the average. The given range, or extent of such deviations, however, merely represents the minimum and maximum extremes of pleural tension. When individual measurements are compared with average figures in order to decide whether or not abnormality is present, allowance must be made for normal deviation. Scientific standards may be conformed to in this regard, if the averages used for comparison are computed by statistical methods applicable to variables.

The object of the present study was to determine the range of normal and abnormal intrapleural tension in artificial-pneumothorax patients.

HISTORICAL CONSIDERATIONS

The technique of artificial pneumothorax has been changed from an empiric to a controlled process largely through the agency of the water manometer and the X-ray. In a recent article, Waring (1) remarks,

John B. Murphy was not only the first American physician (1895) to perform artificial pneumothorax in the treatment of pulmonary tuberculosis, but like-

[1] From the Dispensary Pneumothorax Clinic of the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

wise the first anywhere to utilize the X-ray as an adjunct to collapse therapy. . . . Although Murphy's technique was much like the modern method of giving pneumothorax, it differed in that he used nitrogen gas and he did not have the benefit of a manometer. . . . Forlanini, the Italian physician, who independently performed artificial pneumothorax about the same time as Murphy, did so without the aid of X-ray or manometer.

The earliest manometers in use by pneumothoracists registered in mercury. Owing to the weight of the medium and consequent sluggishness of oscillation, this type of manometer was eventually supplanted by the water manometer. According to Waring, Saugman (1864–1923), a Danish physician, is credited with having introduced the water manometer in Europe in 1907; and Holden (1867–1934) of Denver is on record as the first to employ the water manometer in America in 1909.

It was formerly the custom for authors to present their manometric data in terms of mercury pressure. Since 1 cc. of Hg pressure is equivalent to 13.6 cc. of H_2O, intrapleural pressure findings may easily be converted from mercury to water values. For purposes of uniformity and ready comparison, the mercury pressures of other observers referred to in this paper have been transformed by the author to water pressures.

Donders (2), quoted by Graham (3), was apparently the first to measure the intrapleural pressure in the human being. In 1850, Donders demonstrated that respiration produces a change in intrapleural pressure and that it is more negative at the end of inspiration than at the end of expiration. At the end of quiet expiration he found a pressure of -10.2 cm. H_2O, and, at the end of quiet inspiration, a pressure of -12.2 cm. H_2O.

According to Emerson (4), the first successful determination of the intrapleural tension in a living sound man was made by Aron (5) in 1902. In 36 estimations on one subject he got an average tension at the height of quiet inspiration of -6.3 cm. H_2O; and at the height of quiet expiration, -4.1 cm. H_2O. For inspiration, the maximum reading was -6.9 cm. H_2O, and the minimum, -5.7 cm. H_2O; while the smallest value in expiration was -4.47 cm. H_2O, and the highest, -3.45 cm. H_2O. This applied only to quiet respiration.

McLeod (6), quoted by Sewall (7), obtained a manometric reading in the phase of expiration of -6.8 cm. H_2O; and on inspiration, -13.6 cm. H_2O.

Von Muralt (8), also quoted by Sewall, noted that

After the initial introduction of gas into a pleural cavity which is free from adhesions, the manometer registers an average mean pressure of −6 to −8 centimeters water; in ordinary inspiration it sinks to −10 or −12; in expiration it rises to −4 or −2, and in deep inspiration it may fall to −20 or more.

Snyder (9) observed, "The normal range of intrapleural tension in the adult during quiet respiration varies from −9.5 to −12.2 cm. H_2O with inspiration, and from −4.08 to −6.8 cm. H_2O with expiration."

PHYSIOLOGY OF THE PLEURAL SPACE

Normally, a negative tension, or pressure less than that of the atmosphere, prevails in the potential space between the visceral and parietal plurae. According to Graham (3), this negative or suction pressure is produced by the elasticity and contractility of pulmonary tissues tending to move the lung away from the chest-wall. By virtue of this negative tension, the force of atmospheric pressure operating through the trachea and bronchi makes possible the maintenance of pulmonary expansion. A variation of the potential negative intrapleural pressure occurs during the respiratory cycle. Thoracic enlargement, or movement of the chest-wall away from the lung in the act of inspiration, results in a greater negative pressure, and, on expiration, in lessened negative pressure. On forced inspiration the intrapleural pressure becomes still more negative, and, during forced expiration, still less negative. When communication is established between the pleural space and outside air, as in therapeutic pneumothorax, intrapleural tension is accordingly modified and associated with a certain degree of contraction, elastic recoil, or "collapse" of pulmonary tissues.

SIGNIFICANCE OF MANOMETRIC OBSERVATIONS

In the event that an open needle connected with a water manometer is inserted into the free pleural space, visible fluctuations of the fluid-levels in the tubes of the manometer may be observed. These fluctuations serve as an index of the varying pressure in the pleural cavity during respiration both before and in the course of pneumothorax treatment. Under normal conditions, the manometric fluctuations prior to air inflation are negative in character, that is, they register less than zero on the manometric scale. However, in some cases after the operator has gained access to the free pleural cavity, zero readings may be noted. Such deceptive measurements are usually due to obstruction of the lumen of the pneumothorax needle, or of the "adapter" which is attached inter-

mediately between the needle and the tube joining the manometer. Particles of water, blood, tissue material, or sediment from the sterilizer solution, any of which may act as impediments, can be removed by means of aspiration, or by forcing a small amount of sterile novocaine solution through the needle with the aid of a glass syringe, or after releasing 25 to 50 cc. of air from the air-supply bottle of the artificial-pneumothorax apparatus. When the difficulty has been overcome, negative fluctuations of the manometer fluid will then be revealed.

If the manometer stopcock is allowed to remain open while air is released from the air-supply bottle in the act of inflating a pleural cavity which is under normal negative tension, the negative manometric fluctuations observed before turning on the air are transformed to positive-pressure fluctuations, which, in turn, become gradually less and less positive depending on the amount of air given. The resulting manometric readings noted under these circumstances represent the difference between the positive water-pressure in the siphonage system and the existing negative intrapleural pressure.

When the pleural space is under atmospheric or positive pressure, as in cases complicated by locular adhesions or by fluid, the manometric fluctuations become progressively positive with the introduction of air into the pleural cavity.

Intrapulmonic air injections, on the other hand, are evidenced by small negative to positive excursions of the manometer fluid, averaging -1 or -2 to $+1$ or $+2$ cm. H_2O; by atmospheric-pressure readings, that is, absence of any visible negative or positive fluctuations; or by positive-pressure fluctuations followed by a drop to the zero level of the manometric scale after injection of small amounts of air.

The intelligent use of the manometer will aid the operator in controlling pleural inflation, and preventing secondary pneumothorax complications. Without depreciating the value of the X-ray in pneumothorax work, reliance on manometric guidance will greatly help in dispensing with too frequent and needless roentgenography, especially in established cases of pneumothorax collapse. It is sometimes necessary to perform artificial pneumothorax without the aid of a chest roentgenogram, in which situation the pneumothoracist must be governed by manometric indications. By way of analogy, the pneumothorax technician is occasionally placed in the position of the aeroplane pilot who, under certain conditions, is forced to fly blindly and be guided solely by observations confined to the instrument panel.

METHOD OF INVESTIGATION

The present investigation was conducted in the Dispensary Pneumothorax Clinic of the Municipal Tuberculosis Sanitarium in Chicago. This clinic offers unexcelled facilities for the induction and maintenance of artificial pneumothorax in extramural patients. Antedating December 31, 1933, a total of 13,328 pneumothorax injections, including initial air inflations and refills, were administered to 860 ambulatory tuberculous individuals pursuant to the intensive pneumothorax public health program sponsored by Dr. Frederick Tice and Dr. Allan J. Hruby, members of the Board of Directors of the Municipal Tuberculosis Sanitarium.

With the object of this paper in mind, only those patients were selected for study who showed definite roentgenological evidence of pulmonary collapse following air injection. All manometric readings without concurrent roentgenograms of the chest after pleural inflation were not accepted as data. A total of 4,209 intrapleural pressure measurements, supplemented by X-ray follow-up of 601 patients revealing various degrees of pulmonary collapse following pneumothorax treatment, formed the basis of this work.

Intrapleural pressure measurements were made with a water manometer of the Robinson artificial-pneumothorax apparatus. Only pressures taken at the height of quiet inspiration were recorded. Pressures during the expiratory phase of respiration were excluded from consideration in the present study. Inspiratory pressures were given preference in view of the primary object in artificial-pneumothorax therapy, namely, to secure respiratory immobilization of the affected lung, particularly that of inspiratory excursions.

The manometric readings were obtained by noting the water-level attained in one limb of the manometer at the height of quiet inspiration, and then multiplying the reading by two which represents the true value based on the height of the fluid-levels in the two tubes of the manometer.

In all cases, except pleural-fluid cases requiring aspiration in which thoracocentesis was performed with the subject in a sitting posture, the intrapleural tension was taken with the patient in a lateral recumbent position. A 19-gauge, 2½-inch, rustless steel Vim needle was used for pneumothorax purposes. The site of paracentesis generally selected was one of the lateral intercostal spaces in the axillary region of the chest.

The clinical data of each patient was entered on index-cards bearing the name, age, sex, race, diagnosis, sputum findings, date of air inflation,

amount of air given, and the manometric readings before and after air inflation.

STATISTICAL METHOD

In computing the data relative to intrapleural pressure measurements, the "method of frequency distribution" of Pearson was employed, which permits the determination of the mean or average, and the standard deviation or deviation from the average. The standard deviation is obtained by subtracting each member of the series from the mean, squaring these differences, finding the arithmetical mean of these squares, and extracting the square root. This method, especially applicable to variables, takes into account the modal or most frequent value, and dispersion or scattering of values among all members of the series. If the distribution of such a series were plotted, a curve is obtained known as the "frequency polygon."

The manometric readings were tabulated by frequency distribution, using class intervals of 1-cm. water-pressure, and the mean and standard deviation computed from each distribution. The same method was followed in calculating the amounts of air administered for pleural inflation except that the class intervals were 50 cc. of air. The standard deviation, designated by plus (+) and minus (−) values indicating deviations above or below the average, defined the normal range, that is, the minimum and maximum limits of normal deviation.

The deviation index was utilized in determining the various clinical levels, or range of intrapleural tension. This index is obtained by finding the difference between the actual reading and the average finding, and dividing the result by the standard deviation. The deviation index, signified in terms of plus and minus values indicating deviations above or below the average, defined the boundaries of 5 pressure levels, namely, the range of absolute normal pressures; the range of relative hypotension, and relative hypertension; and the range of absolute or abnormal hypotension, and absolute or abnormal hypertension. Deviations of less than 1 determined the range of absolute normal pleural pressures. Deviations of 3 fixed the inner limits of abnormally low and high pleural pressures, that is, the range of absolute hypotension, and hypertension. Deviations varying between 1 and 3 marked off the intermediate or doubtful zones corresponding to the range of relative hypotension and relative hypertension. Pleural pressures falling within the latter zones belong either to normal or abnormal cases, the exact nature of which is ascertained by clinical or laboratory diagnostic means.

CLASSIFICATION OF PATIENTS

The subjects of this study were arranged from the standpoint of pneumothorax therapy into two major groups, the previously untreated, and the treated cases. Initial, or previously untreated pneumothorax patients were categorically separated into those with a normal pleura, and those with an abnormal pleura. Individuals having a normal pleural cavity, prior to the induction of artificial pneumothorax, served as controls.

All pneumothorax-treated cases were classified into 5 subgroups according to the presence or absence of complicating intrapleural conditions. The first group included patients with a normal or uncomplicated

TABLE 1

Distribution of manometric and roentgenological observations according to clinical groups

CLINICAL GROUPS	TOTAL NUMBER OF PATIENTS	TOTAL NUMBER OF MANOMETRIC MEASUREMENTS	TOTAL NUMBER OF ROENTGENOGRAMS EXAMINED
Control group	428	428	428
Pneumothorax-treated group (control group) included	601	4,209	4,209
Normal-pleura cases	237	2,438	2,438
Pleural-adhesion cases	121	954	954
Pleural-fluid cases	183	548	548
Mediastinal-displacement cases	34	152	152
Combined pneumothorax and phrenic cases	26	117	117
Total	601	4,209	4,209

pleura; the second, those with pleural adhesions; the third, pleural-fluid cases; the fourth comprised patients developing mediastinal displacement; and the last group, individuals with permanent diaphragmatic paralysis following phrenicoexairesis.

The distribution of manometric and roentgenological observations according to clinical groups is shown in table 1.

INTRAPLEURAL PRESSURES PRIOR TO INITIAL AIR INFLATION IN CONTROL GROUP

The intrapleural pressure measurements taken prior to initial air inflation in 428 pneumothorax candidates possessing a normal or uncom-

plicated pleural space served as controls for the pneumothorax-treated cases. The average normal intrapleural pressure at the height of quiet inspiration in the control patients was -8 cm. H_2O, with a standard or normal deviation of ± 2.4 cm. H_2O, and a resultant average normal range of -10 to -6 cm. water-pressure.

The distribution of the manometric readings in the control group classified according to range as defined by the deviation index is revealed in table 2. It will be noted that the majority of the 428 readings, or 67.9 per cent, fell in the range of absolute normal pleural pressures, that is, pressures ranging from -10 to -6 cm. H_2O. Of the total, 13.2 per cent of the pressures were low normal, or relative hypotension pressures, ranging from -15 to -11 cm. H_2O; and 13.4 per cent of the readings represented high normal, or relative hypertension pressures, ranging

TABLE 2

Intrapleural pressure, prior to initial air inflation in control patients, classified according to range as defined by the deviation index

DEVIATION INDEX	CORRESPONDING PLEURAL PRESSURE RANGE (IN CENTIMETERS H_2O)	CLINICAL RANGE	CASES	PER CENT
-3 or over	-16 or over	Abnormal hypotension	24	5.5
-3 to -1	-15 to -11	Relative hypotension	56	13.2
-1 to $+1$	-10 to -6	Absolute normal	291	67.9
$+1$ to $+3$	-5 to -1	Relative hypertension	57	13.4
$+3$ or over	0 to $++$	Abnormal hypertension	0	0
Total			428	100.0

from -5 to -1 cm. H_2O. There was an incidence of 5.5 per cent abnormally low pleural pressures, registering -16 cm. H_2O or over. No abnormally high, or, in other words, no atmospheric or positive pressure readings were obtained in the control patients.

INTRAPLEURAL PRESSURES IN PNEUMOTHORAX-TREATED GROUP

The pneumothorax-treated group comprised 601 tuberculous individuals, ranging from 12 to 68 years of age, the average for the group being 29.1 years. Males and females were equally distributed in the series. White patients predominated, with an incidence of 77.2 per cent, the balance including 22.2 per cent Negro patients and 0.6 per cent Mexicans. Eighty-three per cent of all patients presented roentgenological signs of pulmonary cavitation associated with sputum positive for tubercle bacilli

prior to the onset of pneumothorax therapy. In 50.6 per cent of the treated individuals, the primary, or predominantly affected pulmonary lesion was left-sided; and in 49.4 per cent, right-sided.

A classification of pneumothorax-treated patients according to amounts of air given, and manometric readings before and after air inflation, in terms of average figures, standard deviation, and average range is shown in table 3.

TABLE 3

Amounts of air, and manometric pressures before and after air inflation, in terms of the mean, standard deviation, and average range, classified according to pneumothorax-treated clinical groups

		PNEUMOTHORAX TREATED CLINICAL GROUPS					
		Normal Pleura	Pleural Adhesions	Pleural Fluid	Mediastinal Displacement	Phrenic-Pneumo.	Total Average
Amounts of air (in cc.)	Mean....	500	350	400	400	400	400
	S.D.*....	±150	±50	±100	±150	±150	±50
	Range....	350–650	300–400	300–500	250–550	250–550	350–450
Inspiratory pleural pressure before air inflation	Mean....	−6	−4	−4	−6	−6	−6
	S.D.....	±1.0	±1.0	±3.3	±2.4	±3.7	±1.0
	Range....	−7, −5	−5, −3	−7, −1	−8, −4	−10, −2	−7, −5
Inspiratory pleural pressure after air inflation	Mean....	−4	−2	0	0	−4	−4
	S.D.....	±1.4	±1.7	±3.1	±4.2	±4.0	±1.3
	Range....	−5, −3	−4, −0	−3, +3	−4, +4	−8, −0	−5, −3
Total number of observations...		2,438	954	548	152	117	4,209
Per cent.....		57.9	22.7	13.0	3.6	2.8	100.0

* Standard deviation.

All told, 4,209 manometric and roentgenological observations, respectively, were ascribed to the 601 treated individuals. Pneumothorax injections in their case averaged 350 to 450 cc. of air. The average intrapleural pressure at the height of quiet inspiration, prior to air inflation, ranged from −7 to −5 cm. H_2O; and, after inflation, from −5 to −3 cm. H_2O.

The 4,209 intrapleural-pressure readings following air inflation in the pneumothorax-treated patients, classified according to clinical group and range as defined by the deviation index, is shown in table 4.

Generally speaking, the intrapleural pressure in the pneumothorax-

treated group deviated from normal levels toward the range of either relative, or absolute hypertension. Of the 4,209 pleural pressure determinations, 2,609, or 61.0 per cent, were negative-pressure readings, the majority of which, or 44.7 per cent, were relative hypertension pressures ranging from −5 to −1 cm. H_2O. A total of 1,600, or 38.1 per cent, of all readings represented pressures reaching atmospheric- or positive-

TABLE 4

Intrapleural pressures after air inflation in pneumothorax-treated patients classified according to range as defined by the deviation index

INTRAPLEURAL PRESSURE RANGE (IN CM.) H_2O	D.I.*	PNEUMOTHORAX TREATED CLINICAL GROUPS											
		Normal Pleura		Pleural Adhesions		Pleural Fluid		Mediastinal Displacement		Phrenic-Pneumo.		Total	
		Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Abnormal hypotension, −16 or over	−3 or over	0	0	0	0	0	0	0	0	0	0	0	0
Relative hypotension, −15 to −11	−3, −1	22	0.9	0	0	0	0	0	0	0	0	22	0.5
Absolute normal, −10 to −6	−1, +1	507	20.8	126	13.2	38	7.0	16	10.5	17	14.5	704	16.7
Relative hypertension, −5 to −1	+1, +3	1,316	54.0	332	34.8	141	25.7	38	25.0	56	47.9	1,883	44.7
Abnormal hypertension 0−++	+3 or over	593	24.3	496	52.0	369	67.3	98	64.5	44	37.6	1,600	38.1
Total number of observations		2,438	100.0	954	100.0	548	100.0	152	100.0	117	100.0	4,209	100.0

* Deviation index.

pressure levels, or the range of abnormal hypertension. Seventy-four per cent of the pressures in the latter category were of the positive-pressure type.

INTRAPLEURAL PRESSURE IN PNEUMOTHORAX PATIENTS WITH A NORMAL PLEURA

A total of 2,438 manometric and roentgenological observations, respectively, were attributed to the 237 individuals who revealed an otherwise

normal or uncomplicated pleura during the course of pneumothorax therapy. Refills for the group averaged 350 to 650 cc. of air. The average intrapleural pressure, prior to air inflation, ranged from −7 to −5 cm. H_2O; and, after inflation, from −5 to −3 cm. H_2O. The majority, or 54.0 per cent, of the 2,438 pleural-pressure readings after air injection fell in the range of relative hypertension. A negative-pressure pneumothorax was attained in 75.7 per cent, and a positive-pressure pneumothorax in 24.3 per cent of the 2,438 cases.

INTRAPLEURAL PRESSURE IN PNEUMOTHORAX COMPLICATED BY PLEURAL ADHESIONS

The group of 121 pneumothorax patients with complicating pleural adhesions had a total of 954 intrapleural-pressure measurements and supplementary roentgenological observations. Pneumothorax refills for the group averaged 300 to 400 cc. of air. The average intrapleural pressure, preceding air injection, ranged from −5 to −3 cm. H_2O; and after injection, −4 to 0 cm. H_2O. Fifty-two per cent of the 954 intrapleural pressure readings after air inflation fell in the range of abnormal hypertension.

INTRAPLEURAL PRESSURE IN HYDROPNEUMOTHORAX

A total of 548 intrapleural-pressure readings were credited to the group of 183 patients who showed X-ray evidence of pleural effusion developing in the course of pneumothorax treatment. Refills in these cases averaged 300 to 500 cc. of air. The average intrapleural pressure, before air injection, varied from −7 to −1 cm. H_2O; and after injection, −3 to +3 cm. H_2O. The trend of intrapleural pressure after air inflation in the fluid group was toward the range of abnormal hypertension in 67.3 per cent of the 548 cases. A positive-pressure pneumothorax was the rule irrespective of the degree of lung collapse. Furthermore, it was noted that the largest number of fluid cases appeared in association with a large pneumothorax cavity. Forty-three per cent of the 548 roentgenograms, showing signs of pleural fluid, likewise portrayed complete or almost complete pulmonary collapse.

INTRAPLEURAL PRESSURE IN PNEUMOTHORAX COMPLICATED BY MEDIASTINAL DISPLACEMENT

A total of 152 manometric determinations were made in the group of 34 patients who revealed X-ray signs, as well as clinical symptoms of

mediastinal displacement incident to pneumothorax therapy. Pneumothorax refills for the group averaged 250 to 550 cc. of air. The intrapleural pressure, preceding air inflation, ranged from −8 to −4 cm. H_2O; and after inflation, −4 to +4 cm. H_2O. There was an evident relationship between mediastinal deviation and pleural overdistention. Maximum degrees of pneumothorax collapse were noted in 115, or 75.6 per cent, of the 152 roentgenograms substantiating mediastinal shift. Inflation of the pleural cavity with air, in amount sufficient to cause mediastinal displacement, was attended by elevation of intrapleural pressure toward the abnormal hypertension level in 64.5 per cent of the 152 cases studied.

INTRAPLEURAL PRESSURE IN PATIENTS WITH COMBINED PNEUMOTHORAX AND PHRENIC COLLAPSE

Twenty-six patients, having the benefit of combined phrenic and pneumothorax collapse, underwent a total of 117 manometric and roentgenological observations. Pneumothorax injections for this group of patients averaged 250 to 550 cc. of air. The average intrapleural pressure, prior to air injection, ranged from −10 to −2 cm. H_2O; and, after inflation, −8 to 0 cm. H_2O. A rise of intrapleural pressure after pneumothorax injection toward the relative hypertension level was noted in 47.9 per cent, and continued elevation toward the abnormal hypertension level in 37.6 per cent of the cases under observation.

CONCLUSIONS AND COMMENT

Normally, the negative pressure existing in the potential space between the pleural membranes is variable, becoming more "negative" during inspiration, and less "negative" during expiration.

In the present investigation, attention was exclusively directed to inspiratory pleural pressures in both control and pneumothorax-treated patients.

The normal intrapleural pressure at the end of quiet inspiration in the control group averaged −8 cm. H_2O, with a normal deviation of ±2.4 cm. H_2O. Absolute normal inspiratory pleural pressure, at the height of quiet inspiration, consequently ranged from −10 to −6 cm. water-pressure.

Through the medium of the deviation index, the inner limit of abnormally low intrapleural pressure, or absolute hypotension, was established at −16 cm. H_2O; and the minimum limit of absolute intrapleural hyper-

tension fixed at atmospheric pressure. All positive intrapleural pressures were, obviously, abnormal.

Between the normal and abnormal levels of pleural tension is an intermediate zone, or doubtful zone, including pressures belonging to either normal or pathological cases, the exact nature of which is determined by clinical or laboratory methods. The range of relative pleural hypotension corresponds to pressures varying from -15 to -11 cm. H_2O; and the range of relative pleural hypertension to those registering -5 to -1 on the manometer.

According to the yardstick of values employed in the present study, the normal inspiratory pleural pressures reported by Donders, McLeod, Von Muralt, and Snyder were all relatively low normal, that is, pressures falling within the range of relative hypotension. Aron's findings, on the other hand, based on measurements in a physically normal individual, fell within the limits of absolute normal pleural pressures.

In 4,209 observations of intrapleural pressure after pneumothorax injection in 601 tuberculous individuals considered as a group in the present study there was a deviation of pressure from normal levels toward the range of relative hypertension in 44.7 per cent of the cases; and further elevation of pressure toward abnormal hypertension levels in 38.1 per cent of the cases.

The pneumothorax group, with an otherwise normal or uncomplicated pleura, showed a rise of intrapleural pressure after air inflation from normal levels toward the range of relative hypertension in 54.0 per cent of the cases; and continued elevation of pressure to abnormal hypertension levels in 24.3 per cent of the cases.

In the pneumothorax group with complicating pleural adhesions, elevation of the intrapleural pressure after air injection toward the range of abnormal hypertension occurred in 52.0 per cent of the cases.

The pneumothorax group with complicating pleural fluid showed a rise of intrapleural tension after air inflation toward abnormal hypertension levels in 67.3 per cent of the cases. Such elevation of pressure occurred irrespective of the degree of pulmonary collapse. However, with the development of an excessive pneumothorax cavity an increase in the number of fluid cases was noted. Our observations are in accord with those of van Horne (10), as well as others, that "in cases in which positive pressure has been indicated to accomplish satisfactory compression, a fairly large pneumothorax space, of necessity, has been formed,

and it is the size of the resultant space rather than the degree of the pressure which predisposes to the formation of the exudate."

Pleural overdistention,—a dominant factor in the production of pleural effusion,—likewise contributed to the development of mediastinal displacement. Although mediastinal displacement occurred in the face of a negative-pressure pneumothorax, the majority of cases (64.5 per cent) were linked to a positive-pressure pneumothorax.

In patients with combined pneumothorax and phrenic collapse the intrapleural pressure rose after pneumothorax injection toward relative hypertension levels in 47.9 per cent of the cases; and still further toward the range of abnormal hypertension in 37.6 per cent of the cases. The incidence of cases with negative intrapleural pressure after air inflation was relatively less; and the number of cases with positive pleural pressure was relatively greater in phrenic than in nonphrenic and otherwise uncomplicated pneumothorax cases.

It may finally be concluded that a negative-pressure pneumothorax, that is, one in which the intrapleural pressure is within normal or relatively normal limits, can be attained most frequently in patients possessing a normal or uncomplicated pleura. This type of pneumothorax can, furthermore, be maintained with less probability of secondary pneumothorax complications. The likelihood of a positive-pressure pneumothorax, that is, one characterized by abnormally raised intrapleural pressure, is accentuated in the presence of such conditions as pleural adhesions or fluid, mediastinal displacement, or permanent diaphragmatic paralysis following phrenicoexairesis. Pleural overinflation, culminating in an excessive pneumothorax cavity which, in the majority of cases, is also associated with abnormally increased intrapleural pressure, carries with it the liability to the development of pleural effusion or mediastinal displacement, two of the most common secondary complications encountered in artificial pneumothorax therapy.

SUMMARY

From the standpoint of intrapleural factors in particular, the range of intrapleural pressure variability after air inflation in artificial-pneumothorax patients is determined by the presence or absence of such conditions as pleural adhesions or fluid, mediastinal deviation, and diaphragmatic paralysis due to phrenicoexairesis.

Success in attaining the objectives of pneumothorax therapy with

freedom from operative complications is largely based on the intelligent use of the X-ray and, more specifically, that of the water-manometer.

REFERENCES

(1) WARING, J. J.: History of artificial pneumothorax in America, Jour. of Outdoor Life, 1933, xxx, 347.
(2) DONDERS: Cited by GRAHAM (footnote 3).
(3) GRAHAM, E. A.: Alterations of intrapleural pressure and their significance, Medicine, 1924, iii, 417.
(4) EMERSON, C. P.: Pneumothorax; a historical, clinical, and experimental study, Johns Hopkins Hospital Reports, 1903, xi, 450.
(5) ARON: Cited by EMERSON (footnote 4).
(6) MCLEOD: Cited by SEWALL (footnote 7).
(7) SEWALL, H.: A critique on artificial pneumothorax in pulmonary tuberculosis with special reference to mobility of the mediastinum, Amer. Rev. Tuberc., 1928, xviii, 117.
(8) VON MURALT: Cited by SEWALL (footnote 7).
(9) SNYDER, J. W.: Studies in intrapleural tension, Arch. Surg., 1924, viii, 364.
(10) VAN HORNE, H.: Intrathoracic pressure and pleural exudate in artificial pneumothorax, U. S. Vet. Bur. Med. Bull., 1928, iv, 604.

DESTRUCTIVE PHASES OF INDUCED PHRENIC PARALYSIS IN PULMONARY TUBERCULOSIS WITH CAVITY[1]

PAUL SLAVIN

The majority of pulmonary tuberculous cavities fail to close under therapeutic paralysis of the diaphragm, and some of them grow larger as a result of the operation. Only certain varieties of cavities develop postoperative obliterative tendencies and close in a manner more advantageous than under treatment by other compression methods. The responsive types were described in two previous articles on the subject (1) (2). The purpose of this paper is to discuss four groups of cavernous cases in which phrenic procedures lead to exacerbation of destructive processes.

Group 1: Excavated exudative lesions: The cavities frequently show sputum-levels prior to operation, their draining bronchi being involved in atelectatic processes prevailing in the lesion. Phrenic exclusion increases the tendency of the diseased area to atelectasis, and causes more constant stagnation of sputum in the cavity. Upward compression of the treated lung by the rising paralyzed diaphragm acts as an expulsive force, promoting the separation of disintegrated tissue. Following its initial rise, the paralyzed diaphragm remains stationary for prolonged periods of time. The lesion, with enlarged and deficiently draining cavities, is not being subjected to further compression and continues as an aggravated seat of destruction. Added relaxation, brought about by the cessation of diaphragmatic movements, does not benefit such cavities, as their failure to obliterate is due primarily to a deficiency of reparative processes, and not to mechanical interference.

Group 2: Excavated large fibrocaseous lesions: Rapid spread of cavitation is prevented in such lesions by connective-tissue formation. The rise of the paralyzed diaphragm causes massive expulsion of caseous tissue and increased atelectasis, with resulting enlargement of cavitation and impairment of drainage.

[1] From the New Jersey State Sanatorium for Tuberculous Diseases, Dr. S. B. English, Medical Director, Glen Gardner, New Jersey.

In both groups, *postoperative roentgenograms may simulate obliterating cavitation*, if the shadows of the sputum-filled portion of cavity and surrounding lesion are of same density, or if the antrum becomes screened by overlying shadows of adjacent infiltrated areas, approximated under compression.

In contrast to phrenic interruption, compression provided by artificial pneumothorax, barring complications, can be applied gradually in measured amounts. In excavated exudative and fibrocaseous lesions, artificial pneumothorax, like phrenic paralysis, accelerates the detachment of necrotic tissue and increases cavitation. However, following the destructive phase, continued graded compression of the lung approximates its remaining healthy portions, with resulting obliteration of defects.

Group 3: Large subpleural cavities: These are generally anchored to the parietal pleura and immobilized. Their walls, not being acted upon by the respiratory movements of the lung, grow thick and rigid. The rise of paralyzed diaphragm may cause upward flattening of the cavity-floor, with kinking of the draining bronchus and impairment of drainage. Retention of sputum brings about increased necrotic processes within the cavity-walls, leading to further growth of the antrum and the formation of new foci in its vicinity.

Group 4: Cavities in advanced fibroid tuberculosis: Their walls are prevented from retraction by the rigidity of surrounding connective-tissue infiltrations. The operation obviously does not restore elasticity within cirrhotic lung tissue. In patients with extensive fibroid tuberculosis the vital capacity is usually depleted, and added phrenic paralysis may compromise their pumonary function.

Following is a brief description of cases in which intended artificial pneumothorax was substituted by phrenic paralysis, because of failure to find a free pleural space. Though further enlargement of cavitation could be expected in those cases under treatment by rest-cure alone, the sequence of events showed that paralysis of the diaphragm was responsible for additional damaging processes.

Cases

1: No. 13,409, D.Y., male, aged 22 years. History of left-sided pleurisy with effusion two years prior to admission. Roentgenogram on admission (figure 1), showed cavity, 3.2 x 3.5 cm., situated within an exudative area below left clavicle, near periphery of chest. Because of failure to induce artificial pneu-

Fig. 1

Fig. 2

Fig. 3

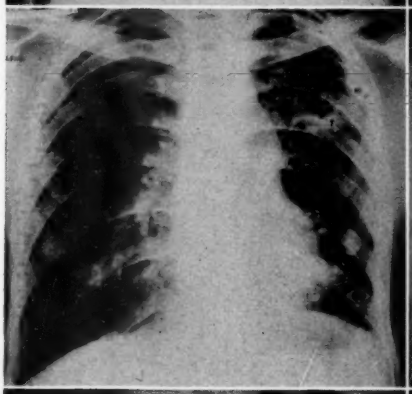


Fig. 4

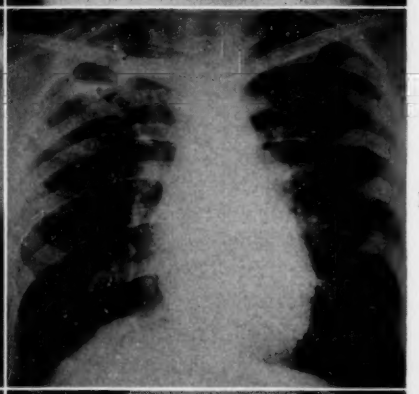


Fig. 5

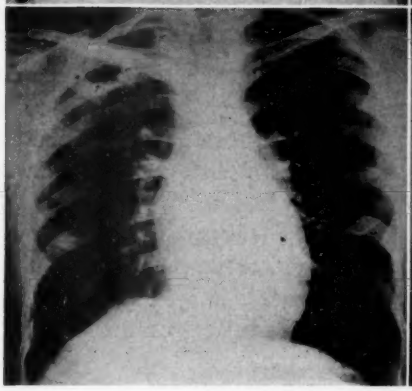


Fig. 6

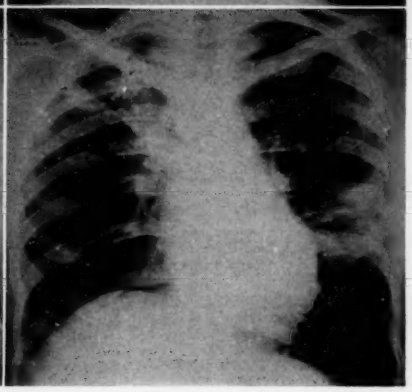


PLATE 1

Fig. 1. Case 1. January 23, 1934.
Fig. 2. Case 1. February 10, 1934.
Fig. 3. Case 1. September 20, 1934.
Fig. 4. Case 2. March 5, 1934.
Fig. 5. Case 2. June 25, 1934.
Fig. 6. Case 2. October 19, 1934.

mothorax, temporary interruption of left phrenic nerve performed. The following day temperature rose to 104 and remained elevated above preoperative levels for six days. X-ray four days after operation (figure 2), showed newly developed massive pneumonic lesion in lower third of treated lung; air-filled portion of cavity, resting on horizontal floor, reduced to 2.2 x 2.5 cm. Forty days later patient developed pleural effusion on contralateral side. His toxic state after operation became aggravated by frequent febrile attacks and by increase of daily expectoration from one ounce to six to ten ounces. The cavity-shadow with level floor continued diminished in size until seven and a half months after operation, when radiograph (figure 3) showed diameters of cavity increased to 4 x 4.5 cm. Two months later diffuse bronchopneumonic lesions appeared in contralateral lung. In this case induced paralysis of diaphragm was followed by immediate massive spread of infection in the treated lung and by continued growth of cavity, obscured in part by overlapping shadows of adjacent lesions.

2: No. 12,588, L.C., male, aged 17 years. On admission (figure 4) right lung showed deficiently draining cavity, 3.5 x 3 cm., situated at level of 1–2 anterior ribs, near periphery of chest, and surrounded by exudative zone. There were additional small punched-out cavities within the dense bronchopneumonic infiltration of right upper lobe. Left lung appeared clear. Satisfactory manometric reading was not obtained in right pleural space and patient continued under treatment by rest-cure alone. Three months and twenty days later, radiograph (figure 5) showed cavity measuring 3 x 3 cm. still having sputum-level. Some of the small cavities were not visible, while one of them, above clavicle, became enlarged to $1\frac{1}{2}$ x 2 cm. It must be noted here that soft-walled cavities show variations in their graphic size depending on phase and depth of respiration during exposure, *cavity-shadow being smaller* and its round shape altered *on expiration.* Condition of patient continued unimproved and temporary interruption of right phrenic nerve was performed. Following operation, patient developed recurrent febrile exacerbations and his expectoration increased from one dram to one ounce per day. X-ray three months and twenty-three days after operation (figure 6) showed cavity enlarged to 4.5 x 5 cm., moth-eaten area below it; and dense pneumonic lesion in left midlung. The operation was followed in this case by extensive enlargement of cavitation and massive spread of infection to contralateral lung.

3: No. 13,414, J.R., male, aged 17 years, Admitted with bilateral upper-lobe cavitation. There was caseous pneumonia of right upper lobe with two subclavicular cavities, 2.3 x 2.5 cm. and 1.6 x 2.5 cm. Left upper lobe showed dense submiliary infiltration with supraclavicular cavity, 1.6 x 15 cm. Right diaphragm 4 cm. higher than left (figure 7). Free pleural space was not found

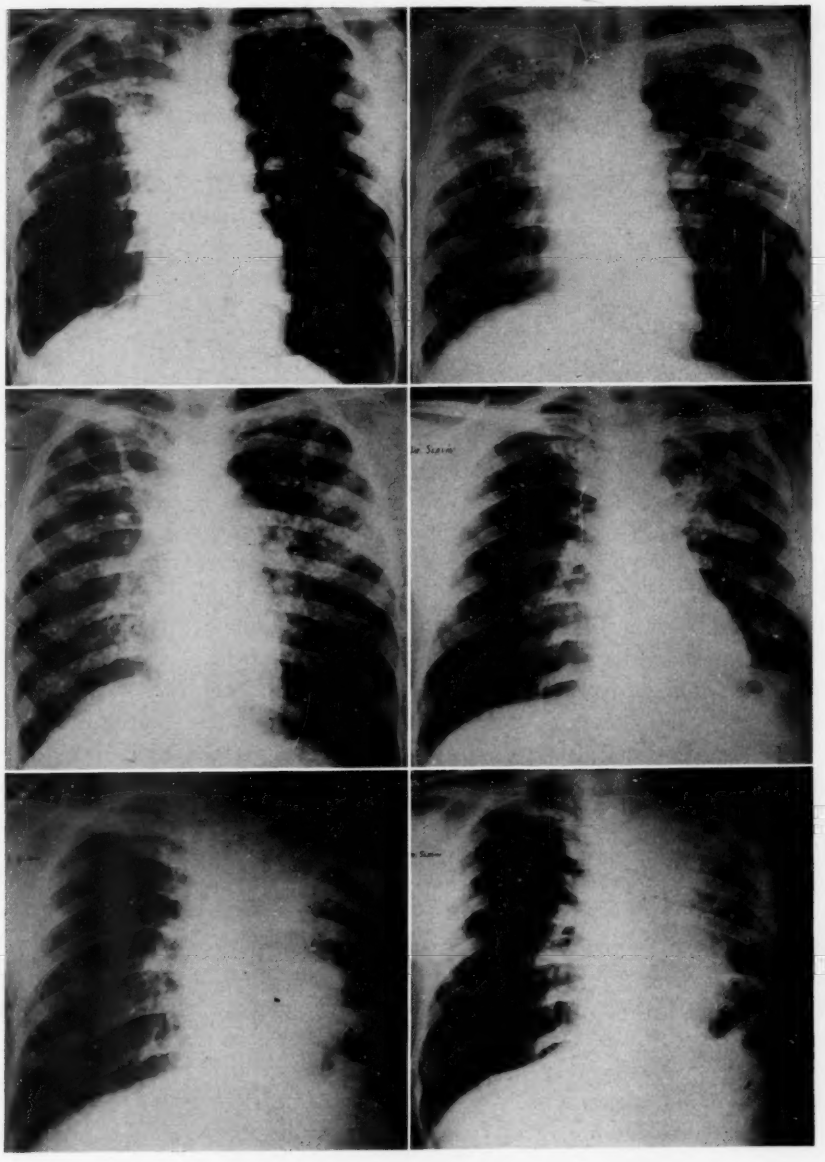


Fig. 7 Fig. 8

Fig. 9 Fig. 10

Fig. 11 Fig. 12

PLATE 2

Fig. 7. Case 3. November 16, 1933.
Fig. 8. Case 3. December 22, 1933.
Fig. 9. Case 3. September 4, 1934.
Fig. 10. Case 4. July 15, 1930.
Fig. 11. Case 4. March 26, 1931.
Fig. 12. Case 4. March 27, 1931.

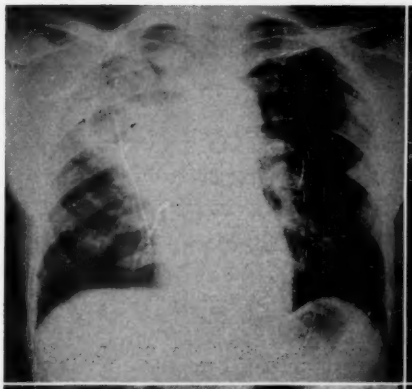
on right, and temporary interruption of right phrenic nerve was performed. Three days after operation (figure 3), lower third of larger cavity was filled with sputum, casting shadow of same density as surrounding lesion; diameters of cavity were increased to 2.5 x 3 cm. Retention of sputum in cavity continued until diaphragm remained paralyzed. Patient developed haemoptysis from treated lung, followed by generalized submiliary infiltration of both lungs. Eight and a half months after operation (figure 9), diaphragm resumed normal function; cavity grew larger to 3.5 x 3.5 cm., and showed no sputum level. This case illustrates postoperative retention of sputum in cavity, simulating obliteration; improved drainage upon return of normal diaphragmatic function; and generalized submiliary involvement of both lungs following haemoptysis, presumably from treated cavitation.

4: No. 11,075, J.E., male, aged 24 years. On admission left lung showed generalized fibrocaseous involvement and extensive cavitation of upper lobe. There was an area of infiltration with possible cavitation in right upper third. Left diaphragm was 2½ cm. higher than right. Artificial pneumothorax on the left having failed, patient continued under treatment by rest-cure alone. Nine months later radiograph (figure 10) showed clearing of right upper lobe and no changes in left lung field. Left phrenicectomy performed, followed by increased expectoration and aggravation of toxic symptoms. Five and a half months later (figure 11), paralyzed diaphragm was 7 cm. higher than right; upper two-thirds of treated lung obscured by shadow of fluid density. Following postural drainage (figure 12), rarefied areas appeared within the dense shadow, showing that cavities were flooded and screened by retained sputum.

5: No. 12,966, A.H., male, colored, aged 20 years. On admission (figure 13) right upper lobe showed exudative lesion with cavity, 3.2 x 4 cm., near interlobar fissure. Diseased lobe proved to be diffusely adherent to chest-wall and did not retract under artificial pneumothorax. Right phrenicectomy performed, following which expectoration became more profuse and toxic symptoms more pronounced. Roentgenogram, eight months after operation (figure 14), showed paralyzed diaphragm elevated 7.3 cm., cavity irregularly outlined and partly obscured by overlying shadows of adjacent lesions. High elevation of diaphragm in this case did not prevent further growth of cavitation and did not promote formation of organized tissue.

6: No. 12,828, J.T., male, aged 39 years. On admission (figure 15) right lung showed giant upper-lobe subpleural cavity, 8 x 7 cm., with sputum-level; fibrocaseous lesions in middle and lower lobes. Artificial pneumothorax having failed, a phrenicectomy was performed. Two days after operation (figure 16) cavity showed a large amount of retained sputum and entire right

Fig. 13



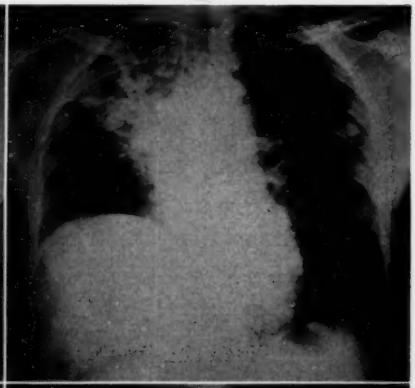
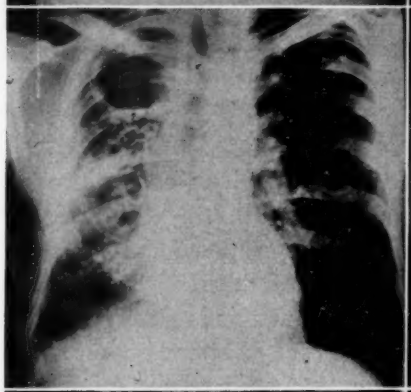


Fig. 14

Fig. 15



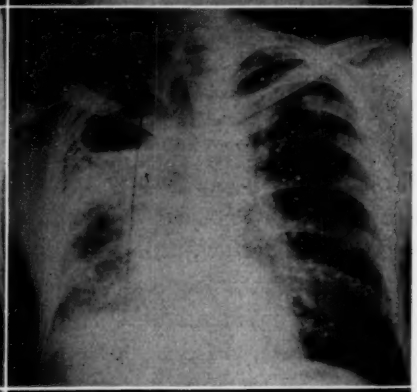
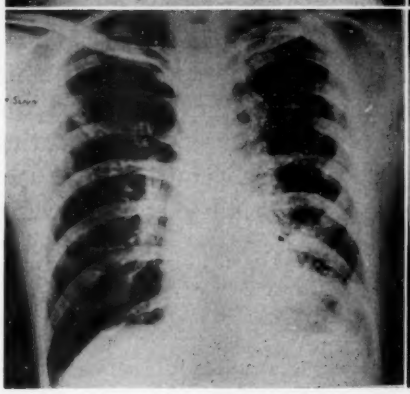


Fig. 16

Fig. 17



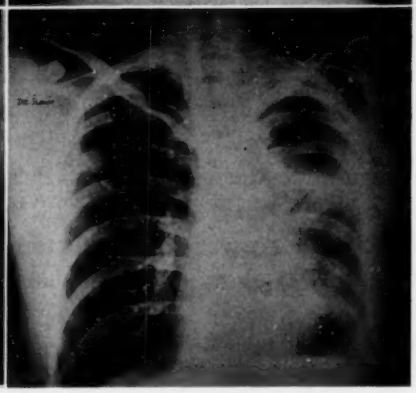


Fig. 18

PLATE 3

Fig. 13. Case 5. January 14, 1933.
Fig. 14. Case 5. December 18, 1933.
Fig. 15. Case 6. October 4, 1932.
Fig. 16. Case 6. December 1, 1932.
Fig. 17. Case 7. August 5, 1930.
Fig. 18. Case 7. October 21, 1930.

lung presented dense shadows of exudative perifocal infiltration. Three and a half months later the paralyzed diaphragm was 7.6 cm. higher than the left; cavity grew deeper; lesions below it were enlarged and of increased density.

7: No. 11,134, G.P., male, aged 31 years. On admission radiograph showed left upper-lobe cavity, 6 x 5 cm., and bronchopneumonic spread in rest of lung. A free pleural space not found on the left, and patient continued on rest-cure alone. Because of progressive enlargement of cavity, phrenicectomy performed seven months after admission. Radiograph, four days after operation, showed (figure 17) paralyzed diaphragm elevated 4 cm., cavity measuring 7 x 6½ cm., and lung markings within its shadow. Operation followed by increased expectoration and aggravation of toxaemia. Two and a half months later (figure 18) cavity increased to 7½ x 8 cm., its shadow more rarefied, showing no lung markings; lesions below cavity were of greater density; diaphragm elevated 7.1 cm.

SUMMARY

Four types of pulmonary tuberculosis with cavity were unfavorably affected by therapeutic phrenic paralysis. Two of them, with excavated exudative and large fibrocaseous lesions, developed postoperative stagnation of sputum in the cavities and accelerated detachment of caseous tissue, resulting in a rapid spread of the cavitation and massive extension of disease. An air-filled portion of a cavity may become obscured after operation by retained sputum or by approximated adjacent infiltrated areas, the *roentgenogram simulating postoperative obliteration of cavity.* In large subpleural cavities, representing the third group, phrenic paralysis causes impairment of drainage, leading to progressive destruction within cavity-walls. In cases with excavated advanced fibroid tuberculosis, forming the fourth group, there may be a dangerous postoperative reduction of their depleted vital capacity. In all four groups, high elevation of a paralyzed diaphragm does not seem to diminish the untoward effect of the operation.

REFERENCES

(1) SLAVIN, P.: Closure of adherent pulmonary tuberculous cavities by combined artificial pneumothorax and phrenicectomy, Amer. Rev. Tuberc., 1933, xxvii, 355.

(2) SLAVIN, P.: Changes in pulmonary tuberculous cavities resulting from induced paralysis of the diaphragm, Ibid., 1934, xxix, 629.

AN IMPROVED FORCEPS FOR OPERATIONS ON THE PHRENIC NERVE[1]

J. W. CUTLER

Crushing of the phrenic nerve or its evulsion are operations of established value in the treatment of pulmonary tuberculosis. The instrument illustrated simplifies these procedures and makes it possible to perform either with the same instrument, at the same time increasing the safety factor. In crushing the phrenic nerve with the usual instruments found in the operating room, it not infrequently happens that the nerve is accidentally cut by the serrations of the forceps, which are usually too sharp and too deep. Also only a small part of the nerve can be

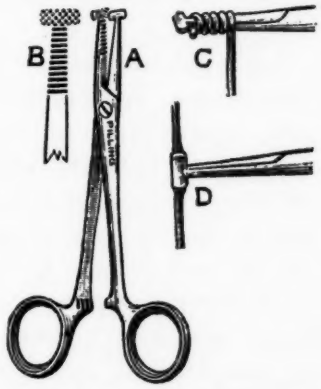


FIG. 1. See text for description[2]

crushed at one time. In the forceps illustrated the serrations are just deep enough to crush the nerve smoothly and uniformly. The wide cross-piece crushes the nerve over a considerable area, and only a few applications of the instrument are necessary. (Figure 1, D.)

When a permanent paralysis of the diaphragm is sought by phrenic evulsion, the nerve is severed and the desired section of the nerve pulled out of the wound by winding it about the shank of the forceps with a steady firm traction upward. The cross-piece of this T-shaped instrument prevents the nerve from slipping off. (Figure 1, C.)

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] This instrument is made by The George P. Pilling & Son Co., Philadelphia.

THE CHANGES IN PATHOLOGY OF PULMONARY TUBERCULOSIS AS A RESULT OF TREATMENT[1,2]

HENRY C. SWEANY

Tuberculous lesions, like most other biological phenomena, have an evolutionary development. They form; they advance to maturity; and, if the patient survives their progressive phases, they undergo regressive changes toward healing. In the strict sense of the word, there is no such thing as a pathologically inactive tuberculous lesion. The change is either progressive toward maturity, or retrogressive toward healing. Even after complete "clinical" healing, the caseation and calcification undergo slow absorption and the fibrous tissue gradually becomes more dense.

In the maturation of a tuberculous lesion, the course pursued is different under different circumstances. Sometimes it means a lesion with fully developed inflammatory capsule at the end of its progressive phase; or it may mean excavation, depending on the size of the original focus or the proximity to a bronchus. A small focus in which an equilibrium has been reached early between the host and the parasite, that is, when the advance of the parasite has been checked by the cellular barrier and walled off, will become encapsulated and go on to a healing by caseation, calcification, and even ultimate resorption. A focus in which the equilibrium is not reached early, however, will spread to such a size or fuse with other tubercles so that encapsulation may become difficult because of the proximity of larger bronchi which facilitate excavation. In this type and in the larger infiltrative foci resulting from great "dosage" or a pneumonic spread, there is usually excavation. When healing takes place in the presence of cavities, it is much more complex because it involves the closure of the cavities.

All tuberculous infections, therefore, run their course: some quickly, some slowly; some intermittently progressive, stationary, or regressive, depending upon the type and dosage of bacilli, type, age and condition

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Presented at a meeting of the Mississippi Valley Sanatorium Association, Cedar Rapids, Iowa, September 27, 1934.

of the host; and, most important of all, the type of the host's "environment," as suggested and discussed by Krause (1).

This environment includes the various factors that assist nature in stopping the progress of the disease; or, on the contrary, the unfavorable type that adds fuel to the flame. It is as variable as life itself. An adequate diet, eaten regularly, regular sleep and rest, and a vocation or routine of light work and short hours, with a minimum of mental strain or worry, are generally favorable, and will permit many patients to carry their disease sometimes for years without any regular treatment. Undoubtedly, many of these result in spontaneous cures, as indicated by healed lesions in patients dying of other causes. However, overindulgence in work, or deprivation, exposure, or accidents, will only too often bring the patient to the active disease more quickly, when some form of special treatment must be instituted for an arrest of the process.

The age, race, and condition of the host is of a widely variable character. The infant, the adolescent girl, the parturient mother, the aboriginal races, or the underfed, are considered to be of greater susceptibility than other types.

The parasites may vary either qualitatively or quantitatively,—the latter being the more important. If the seeding of bacilli is small and the host lives a moderate life, the result may be no more than an incidental focus producing no symptoms and little pathological change. If the original focus is large, or some accident or incident occurs that will depress the powers of resistance, a spread, releasing activity, may take place.

The interplay of these and many other factors, is subject to a wide range of variations, and, above all, is governed largely by chance. This accidental or haphazard nature of the disease has been well expressed by Krause (2) when he says, "At its culmination every case of tuberculosis represents, in some degree, the fruition of a long sequence of accidental circumstances."

While the evolution of the disease may go through the usual stages and produce various forms of healing spontaneously, it is more the purpose of this paper to describe some of the pathological manifestations of healing that have been observed to take place under controlled treatment, because in this manner a better estimate may be ascribed to the particular result. There is no occasion here to discuss in detail the well-known pathological phenomena of tubercle-formation and the regression of either primary or postprimary tubercles. There are changes in heal-

ing, however, that are not thoroughly appreciated. These will be described.

The common observation in healing pulmonary tuberculosis is not a simple and uniform process. Sometimes there is represented a progressive phase in one place, with healing in another; and either one of these may represent varying degrees of rapidity of formation and evolution. The common finding is that of a beginning process in the dome of the lungs (most frequently along the subapical bronchi). These lesions may heal completely or they may spread downward and forward, step by step, from one bronchus to another, becoming smaller in size and younger in age as they progress toward the base. A spread to the opposite side may be early or late, mostly apical, but frequently to midlung, and many times basal, or to the apex of the lower lobe. The upper and older lesions usually ulcerate and present cavities in different stages of evolution. Some, however, may show signs of healing. An arrest of the process may occur at any time. In the event of an arrest or a regression of the lesions, there is first a resorption of the most exudative aspects, including the perifocal inflammation and much of the removable cellular infiltrates. The caseous portion of the centre is not affected at first, but may become more completely encapsulated. Later, this *caseum* may, and usually does, become calcified, similarly to what is observed in primary tubercles; and this calcification may remain throughout life, gradually resorb, or become sloughed out into cavities. Rarely do secondary tubercles become ossified as do the old primary lesions. Sometimes smaller lesions do not calcify, but become permeated with capillaries proceeding from without, and be resorbed completely, leaving only small fibrous scars containing many blood-vessels.

The perifocal inflammation and the very small foci that have not formed extensive caseation, become resorbed and apparently are healed without leaving any permanent damage. The appearances here, from clinical and X-ray standpoints, are, however, deceiving; and there are practically no tuberculous lesions that are ever resorbed that do not leave varying amounts of damage to the tissue involved: so that the old dogma of "no *tubercle* without a trace"—however minimal and frequently microscopic—is probably correct. The immediate perifocal area around the individual tubercles or the clusters of acinonodose tubercles, although it may appear relatively clear on X-ray, is actually damaged lung tissue so far as gaseous exchange is concerned. Sometimes its function is impaired beyond any usefulness. The elastic tissue is

damaged; the walls of the alveoli become fibrotic; the capillaries disappear; the alveoli become distended through inspiration and lack of elasticity; and all this results in a condition of emphysema which is so commonly found in patients having arrested or quiescent advanced tuberculosis. It may be stated that the ultimate recovery of every patient depends to a large extent upon the amount of lung tisssue that remains unimpaired by tuberculous inflammation and the latter's residua. True, those patients with a vast amount of involvement may live; but, as time goes on, they develop an intractable dyspnoea because of destruction of the available aerating surface of the lung. This distressing complication, as well as other related clinical and roentgenological aspects, have been clearly described by Dunham (3).

Much of the perifocal inflammation is made up of serofibrinous exudate, with a scattering of cellular elements. When such a finding is isolated, it is called *gelatinous pneumonia*. However, the immediate periphery of the tubercle displays more cellular inflammation, and, no doubt, this causes greater damage than results at the extreme periphery of an involved region; yet it seems that even the tissue affected by only the gelatinous pneumonia is permanently injured, and will show the marks of this injury when resorption takes place. This fact leads one to suspect that in a tuberculous exudate there is something that is not present in any other type of pneumonia. The effect of tuberculous allergy, or whatever may be the process, is more detrimental than are exudates of many other infectious diseases.

The macroscopic manifestation of such a resolution may be suspected when there is a marked depigmentation of the pulmonic tissue. Especially is this true when there is a sharp line dividing the lung-field into a gray upper part and a more reddish-brown lower part, with small patches of gray around the remnants of the old isolated foci in the lower half. It is true that, without infection, some lungs are naturally a uniform gray, but there is a "dead" grayish cast to the resolved part which gives it distinction. Another feature of this affected gray area is its "dead" feeling. It is dry, stiff, and spongy to the touch. In advanced conditions the section reveals a "shredded-wheat" appearance. Finally, the alveoli are dilated from but faintly perceptible size to patches of bullous emphysema, sometimes several centimetres in diameter. In one of our specimens there was a bulla 12 x 15 x 18 cm.

Microscopic appearances are even more distinctive than are gross features. Here the alveoli, the atria, the alveolar ducts, and the re-

spiratory bronchioles may be found enlarged,—from a faintly perceptible enlargement, with hypertrophy of muscle-fibres, to complete obliteration of all structural markings. The dilatation may be so extreme that the tissue takes on the appearance of a cystic lung.

In alveoli of the greatest dilatation, the walls may be thinned-out to hair-like fibrous cords with no visible blood-supply. More commonly, the alveolar walls are thinned to fibrous plates with few or no capillaries present. The blood-supply in this stage is confined to the interalveolar junctions. As the dilatation becomes more extreme, the smaller vessels are gradually destroyed, so that many times only the larger arterioles remain to furnish blood-supply. Obviously this adds little or nothing to the aerating surface of the lung. And, in this connection, we should remember that throughout its development specific tubercle is an avascular process.

The roentgenological appearance of this type of involvement may be quite misleading. Even postmortem roentgenograms fail to reveal anything more than a thinning-out and an occasionally "shredded-wheat" appearance reflecting expanded lung tissue shot through by fibrosis in the perilobular, peribronchial, and perivascular spaces. Such a thinned-out lung with evidences of contraction into the apices, and a "weeping-willow" drooping of the bronchi, with indications of "tenting" of the diaphragm, are signs that point to this condition. When coupled with dyspnoea and classical clinical signs, it makes the findings more certain. As dyspnoea becomes marked, the emphysema also involves normal alveoli damaged only by mechanical stretching. This may be distinguished from the other form in that the distension is more uniform: there are no signs of former disease, and the coloring is better preserved. (Plate 1.)

Another common late result of healing tuberculosis is bronchiectasis, particularly in the upper lobes, although not exclusively so. It may be found in any stage of the disease, even early when only a few tubercles are found toward the ends of the bronchi. Frequently tubercles remain in communication with bronchi, or they may, after partial healing, become reopened into the bronchus, to produce a small "loop" or "indian-club" cavity that gradually leads to a bronchial dilatation set up by the flow of toxic material down the walls. These slight bronchiectatic dilatations are prone to produce changes in breath-sounds that are frequently heard in early tuberculosis.

The most exaggerated type of bronchiectasis is usually seen when there

Fig. 1

Fig. 2

Fig. 3

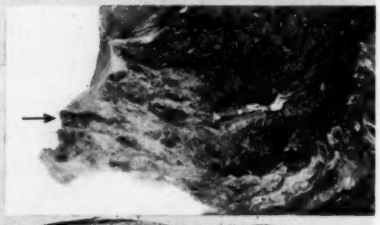


Fig. 4

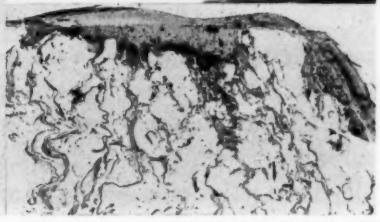


Fig. 5

PLATE 1

Fig. 1. Roentgenogram of patient W. F., revealing an old fibroulcerative tuberculosis at the apices, with a loose network of stringy shadows on the right and a marked decrease in the normal density on the left.

Fig. 2. A gross picture, showing the size and character of the bullae.

Fig. 3. A midsection of the lungs, revealing the fibroid apices with bronchiectasis, the dry spongy tissue in the midzones. The bullae are collapsed and do not show.

Fig. 4. A "close-up" of the spongy tissue and dilated bronchi in the left midzone.

Fig. 5. A low-power magnification of a microscopic section, revealing long shreds of tissue with no remaining alveoli. × 4, H. & E.

has been a marked amount of infiltration around bronchi. This infiltration may be caused by peribronchial or perivascular disease, producing lymph-stasis and even exudation into the involved segment of lung, and resulting in a partial collapse of the involved lung tissue, to give a gross appearance of carnification and a considerable amount of shrinking in volume. The vascular supply is also impaired, and the whole segment becomes infiltrated with fibrous tissue. Some have applied the term *atelectasis* to this condition, although I believe with Fletcher (4) that the concept *atelectasis* should be confined to congenital unexpanded lung tissue, and that a much more appropriate term is "detelectasis," even though this is new to the literature. By this term Fletcher means the collapse or partial collapse of lung tissue resulting from some active disease-process such as influenza or tuberculosis; while he restricts *atelectasis* to that type of unexpanded lung tissue that occurs at birth. The bronchi that penetrate this collapsed and diseased lung tissue, especially when they have remained open, are subject to bronchiectasis just the same as in true atelectasis, in which the result may be a congenital bronchiectasis or cystic lung, depending on whether it is lobular or lobar in origin. Many times the parenchymal excavation may produce cavities of considerable size that exist for years, and become almost, if not entirely, closed. Yet the bronchiectatic dilatations have a tendency to become more marked. The usual bronchial pressure during coughing, and even in normal respiration, is greater than that coming through the consolidated lung tissue surrounding these bronchi. The peribronchial tension due to fibrosis may also play a rôle in the advanced disease, in the true sense of Corrigan. The presence of cartilages in the bronchi further help to prevent them from becoming collapsed and healed, so that the result is a continuous dilatation. Many times these large bronchi will radiate from the hilum like spokes of a wheel, filling almost entirely the whole space out to the cavities in the parenchyma. (Plate 1, figure 3.)

This leads us to a discussion of the closure and healing of tuberculous cavities. This question has been discussed by many authors since and including Laennec. One of the most recent ideas is that of Coryllos (5) (6) (7). This author suggests that the closure of cavities is brought about, first, by the closure of the bronchus; and that, when the bronchus is definitely closed, the air will be absorbed from the cavity, which will then close of its own accord. This line of reasoning seems to be rational, because it is a known fact, first shown by Lichtheim (8), that air enclosed within the lung (or pleural cavities) will soon be taken up by the blood-

stream, provided the circulation is intact. There are only two things that can happen: one is an absorption of air, with collapse of the cavity; and the other is the filling of the cavity with fluid. As elsewhere, here too Nature "hates a vacuum."

Just as closure of a bronchus will lead to a collapsed cavity, many times the bronchi are buckled or they protrude into a cavity in such a manner as to form a valve, continually admitting air on deep inspiration, and withholding it. As dyspnoea in this type of patient becomes worse, the result is a balloon-like cavity that may become very large and sometimes actually rupture into the pleura. (Plate 4, figures 1, 2, & 3.)

There is, however, more to the closure of cavities than the question of closure of bronchi. There are at least two other natural avenues of healing of the cavity in addition to this. The more important of these two is the deposition of fibrin between layers of pleura that, upon organization, contracts the cavity within the lung. The other type is the accumulation and organization of granulation-tissue on the inner wall of the cavity. Just as the spread of the cavity may be caused by a continual caseation and sloughing of this inner wall, so the contraction of the cavity may result by an encroachment of this granulation-tissue upon the lumen of the cavity.

There is still another little-mentioned type of pathological change in the extreme types of pulmonary fibrosis. This results from the contraction of fibrous tissue that thus produces a distortion of the great vessels, the trachea, bronchi, ribs and spine. After marked fibrosis in the upper part of one lung, the ribs will appear pulled together, and the spine pulled over; and the trachea and the bronchi will sometimes be pulled toward the affected side. More important than any of these end-results, however, is the fact that the great vessels may be buckled or pressed upon by this fibrous contraction. It is not unreasonable to suspect many times that this will produce cardiac embarrassment or functional manifestations of disturbance of the heart. This has been forcibly emphasized by Sewall (9).

Apart from these changes that occur during the rest-treatment of tuberculosis, the most radical changes have been observed to result from the various forms of special treatment. First, under this heading, we shall discuss some specifics that have been used, the most important of which is tuberculin. There is no doubt that, in the use of tuberculin, changes are produced in and around the tubercle, that perhaps result in an increase of the production of chronic granulation-tissue. However,

there has been no convincing pathological work on the late effects of tuberculin around pulmonary lesions, although the Saranac Laboratory "school" have pretty well described and explained these perifocal, focal and constitutional effects. It has long been known and it has later been observed roentgenologically that tuberculin will cause an increase of exudation around pulmonary lesions. Such changes, if sufficient, have been considered as setting up focal reactions. In the event of healing of this type of reaction, therefore, there is every reason to believe that there will be an increase in chronic granulation-tissue with its subsequent fibrosis. The advocates of tuberculin therapy have carefully pointed out that tuberculin will only produce favorable effects in the more chronic and afebrile type of patient that is not showing acute manifestations of the disease. It has been especially recommended in bone and lymph-node types, when stimulation of fibrosis is a desirable factor, as well as old chronic cases that show little absorption of toxic products. By mild forms of graduated exercise, such patients have undergone treatment successfully with their own or "autotuberculin." No doubt, much of the fibrosis resulting in and around tuberculous lesions is a result of the action of "autotuberculin" stimulation. (However, the term *autotuberculin* should not be regarded as representing a product of the nature of standard "tuberculin.")

Somewhat similar in its action to that of tuberculin seems to be the effect of gold salts in the treatment of tuberculosis. In this instance there is more tangible pathological evidence. Although it has been fairly well established that gold salts do not kill the bacilli in the body, yet they do in certain types of patients produce a perifocal stimulation of fibrous tissue that many times leads to favorable results,—an action that was first suggested by William Pepper of Philadelphia many years ago. These observations have been briefly mentioned by Henrichsen and his associates (10) (11) in publications from this institution, concerning the effect of sanocrysin, one of the most widely used gold salts. Since any bactericidal effect of Sanocrysin has been found by Calmette (12), Watanabe and Sato (13), and others, to be of little or no potency, the question naturally arises as to what is the cause of any favorable changes in the patient. Based upon findings of Levinson and Petersen (14) in lymph-fistula experiments on dogs, it has apparently been shown that sanocrysin behaves in a manner quite similar to that of tuberculin. First, sanocrysin causes a stimulation of the reticuloendothelial system, which sets up an increased permeability of the lymphatics; but this is

immediately followed by a decreased permeability and a blocking of the lymphatic system. Such a physiological effect affords a workable theory to explain the action of the drug in human tuberculosis, because in the clinical management of the treatment there is an effect that parallels this experimental work. First, there is a toxic effect, the result of increased permeability with its liberation of toxins, to be followed by a rather sudden cessation of symptoms corresponding to a decreased permeability.

It was the view of the original authors of sanocrysin that the toxic effect originated from tubercle bacilli killed by the drug,—a view that was soon proved to be fallacious; but we are not sure that some of this action may not be due to a liberation of toxins. In the larger doses, however, we feel that it is principally the effect of metal poisoning, or of tissue susceptibility to the gold salts. In the work in this institution there have been some ill effects following the employment of sanocrysin, although it is doubtful if there were any that resulted directly from its use. In studying this pathological material we have been able to observe certain changes that seem to point to a definite action of the drug. Two of these cases we shall cite, one in which the treatment had been finished only recently, and the other after about four years. In a patient who died soon after the treatment (after a preliminary improvement), there was evidence of a marked perifocal stimulation of granulation-tissue. There has also been observed an increase in monocytes of the blood that is compatible with this type of stimulation. In some patients these cells were so greatly increased that it indicated an overdosage. Perhaps the greatest change in the capsule of tubercles was the marked increase in the number of capillaries around their walls. There was virtually a solid bed of newly formed capillaries extending from the outer wall to a distance almost twice the thickness of the wall of the capsule itself.

The other patient was one that died four years after the treatment, as a result of a terminal amyloidosis. There was a marked amount of healing in the lungs of this advanced case of tuberculosis; there were also very few newly formed tubercles. There were, moreover, extensive areas of granulation-tissue and islands of fibrous tissue that indicated the former presence of tuberculous inflammation. Although this chronic type of involvement was no different than that observed in any other advanced type of healing tuberculosis, yet the time of its formation seemed to be shorter than that commonly found.

Of all the numerous other remedies that have been recommended, including the cinnamates (*Hetol*), creosote, iodine, etc., only iodine has been studied so far as its effect on the body is concerned. The iodides have long been known to have a favorable effect upon the blood-vessels. Jobling and Petersen (15) have shown that they suppress the antiferments of the blood, allowing to the ferments a greater activity. The favorable action claimed from this type of medication may well be understood in vascular disorders, in which a better circulation is desired; but usually such an action is frowned upon in tuberculosis in which a better encapsulation, and not a softening or lysis, of tubercle is desired. After all, "healing" in chronic tuberculosis means fibrosis, repair and scarring.

Of the many changes that occur in the evolution of tuberculous disease, the healing changes during collapse therapy are perhaps the most outstanding, because here a maximum of effect is realized in a minimum of time. Owing to the fact that collapse therapy is a relatively recent procedure, there has been but a limited opportunity to study its resulting anatomical changes. While there may not necessarily be any new pathological reactions produced, nevertheless, as a result of the changes in anatomy and physiology brought about by the respective forms of collapse, we should expect to find changes as a result of and proportional to the degree of collapse.

The fundamental changes during pulmonary collapse are relatively simple, amounting to a shrinking of the alveolar spaces and a thickening of the alveolar walls; but the associated pathological changes, including evidences of healing, and especially the mechanism of certain types of spontaneous collapse, are more involved and require special attention. This should involve especially the various forms of massive collapse and atelectasis, about which much has been written, but there is still much speculation about causes, mechanisms and classifications.

Of all those who have treated of this subject, it seems that the previously mentioned classification of Fletcher (4) comes closest to satisfying all the conditions. This author divides the field into four groups. He restricts the term *atelectasis* to that form of collapse originating at birth because of a lack of filling of alveoli. This confines the term to its true and original meaning, and avoids confusion over such forms of collapse as may be caused by the association of acquired disease. Atelectasis may be either lobular or lobar: the former leading ultimately to a cystic lung, and the latter to congenital bronchiectasis, the various dilatations depending upon the size of the bronchial unit involved.

The second group Fletcher calls *apneumatosis*, or an airless lung produced by a simple mechanical plugging of a bronchus. This form results from the occlusion of a bronchus by a foreign-body, blood, mucus, etc., and corresponds to the *passive* massive collapse so well described by William Pasteur (16).

To the third group Fletcher gives an entirely new term,—*detelectasis*,—one that is expressive and that seems to merit a permanent place in our nomenclature. Under this grouping he considers the little understood *active* collapse of William Pasteur, and that form of collapse produced by diseases like tuberculosis, influenza, and pneumonia, in which there is a mixed process involving both a relative alevolar collapse and pathological infiltrations of serum and chronic types of cellular infiltrates. Finally, there is *pneumothorax*, which may be divided into spontaneous and artificial.

It seems, therefore, that there are several clear cut types of pulmonary collapse, which we shall briefly summarize. There is the passive and active massive collapse; true congenital atelectasis; an acquired or false atelectasis due to disease; and hydrothorax, haemothorax, pyothorax and pneumothorax. To this last group we may add the various surgical procedures that have been used and are being used to collapse lungs therapeutically, as well as the spontaneous collapse that results in healing diseased tuberculous tissue. The surgical measures only will be dealt with here because they alone give us any groundwork for comparison of results.

Since the discovery of the value of air compression of tuberculous lungs, there has resulted an enlarged scope for pathological study. The healing of the tuberculous tissue following artificial collapse has not been extensively studied pathologically, notwithstanding the numerous reports that have been made clinically.

Plate 3 shows the progress of a patient having artificial pneumothorax over a period of years. The patient died of a peritonitis following a rupture of the appendix. The figures illustrate healing as a result of collapse therapy, side by side with natural healing. The lower cavity healed completely within one year's time because it was subjected to artificial collapse, while the upper cavity held open by adhesions was incompletely closed after four years.

The complications include those of the operation itself and those due to some turn in the course of the disease. Empyemata, almost universal with spontaneous pneumothorax, should run less than 10 per cent in artificial pneumothorax. Interstitial emphysema is occasionally en-

countered. The most dreaded complication of this treatment, however, is the accidental air-embolism that occurs occasionally and usually leads to sudden death. If the emboli have not lodged in a vital centre, the patient may recover after a syncope of varying periods of time. Out of the sudden deaths accompanying the instillation of gas, in our institution over the past fifteen years, we have had the opportunity to study five by postmortem examination. We definitely found gas bubbles in the heart or cerebral vessels, or both, in three cases, and suspect that

PLATE 2

Fig. 1. Postmortem roentgenogram of patient B. J., who died of amyloidosis following an incomplete thoracoplasty. Note the calcification on the right with the collapse of the left base. The first rib, however, subtended a cavity in the apex.

Fig. 2. A high-power microphotograph of a reticulum stain of a section taken of the base of the collapsed lung, revealing reticulum fibres spreading out into the collapsed tissue, with numerous lymphocytes. × 215, H. & E.

PLATE 3

Fig. 1. Roentgenogram of patient J. M., taken May 12, 1925, revealing retouched cavities in the right upper.

Fig. 2. The postmortem roentgenogram, taken four years later, after patient died from peritonitis following a ruptured appendix. Only one small reniform cavity remains in right apex.

Figs. 3, 4, 5 & 6. Reveal the appearance of the cavities at different periods during treatment with pneumothorax. Note the lower cavity that was affected by the collapse, closed completely in about a year's time. The upper one, that was held open by adhesion, pursued a slower course in closing, being only about two-thirds closed within four years.

Fig. 7. Reveals a section anterior to the main bronchi, showing the puckered scar of the healed cavity.

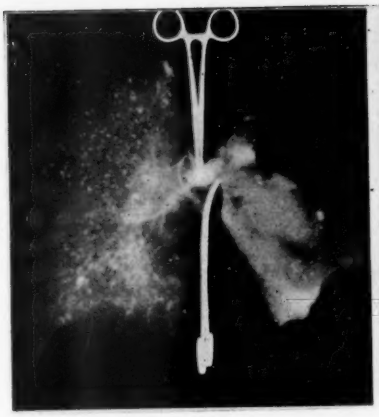
Fig. 8. A section through the middle of the bronchi reveals the fibrous walled cavity in the apex still open.

Fig. 9. Represents a low-power microphotograph of the scar-tissue of the healed cavity. Note the mass of fibrous tissue containing many capillaries. × 3, H. & E.

the other two died of the same cause. In one patient the gas was instilled beneath the visceral pleura and gradually stretched the veins going to the pleura to the breaking point. As soon as rupture took place, the air immediately was sucked into the pulmonary veins and thence to the major circulation.

Next to this accident we list accidental needle puncture of the lung, resulting in a valvular pneumothorax that will, if not treated, lead to death. It has happened in several of our patients, three of whom died and came to autopsy. In these patients the accident happened to the only remaining good lobe, so that the treatment of drawing out air

Fig. 1



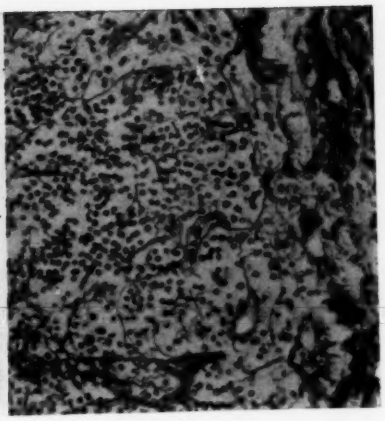
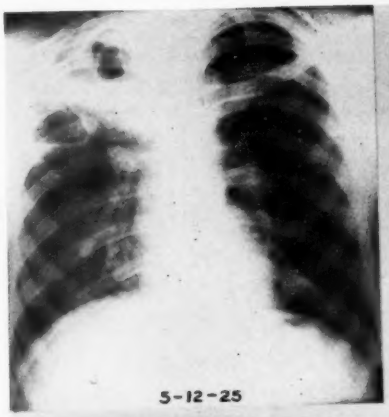


Fig. 2

PLATE 2

Fig. 1



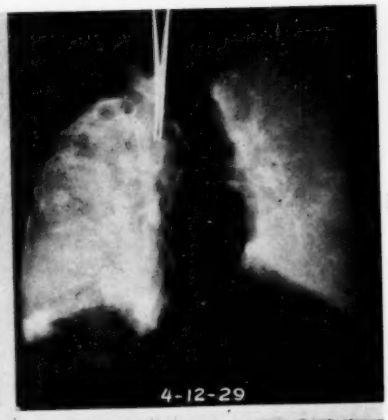
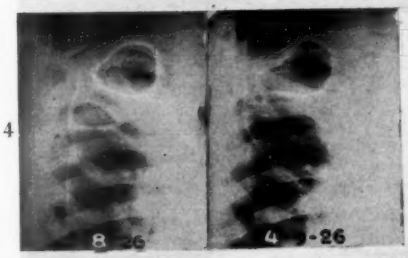
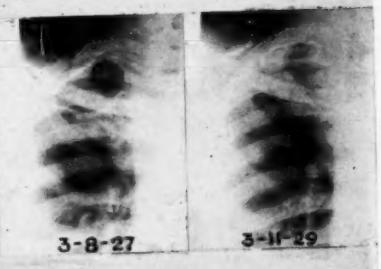


Fig. 2

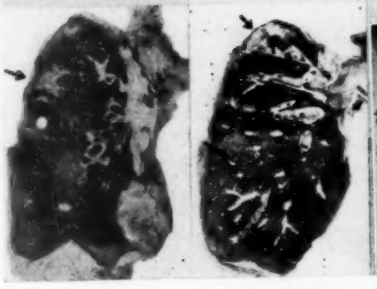
Figs. 3 & 4





Figs. 5 & 6

Figs. 7 & 8



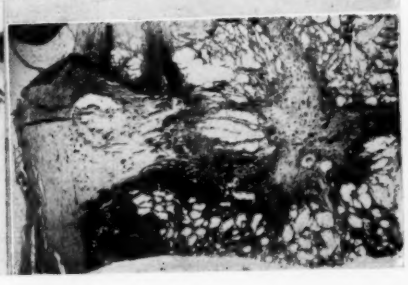


Fig. 9

PLATE 3

proved of no avail. Others have been saved by drawing out air or leaving a needle in connected with a tube having a few millemeters of pressure. (Plate 4, figures 4, 5 & 6.)

Pleural shock, that has been blamed for many deaths, still remains to be proved, *as a cause of death,* although there is no doubt that it is frequently a serious complication leading to pain and syncope. Usually the history is different from that of air-embolism in that the complaint may begin when the needle first enters before there is any gas given or before there is any chance of producing a bronchovenous fistula.

Due to the fact that it is practically impossible to demonstrate any tissue change in this condition, it leaves a great deal to speculation.

There is another complication that seems to be a possibility and even a probability, in certain cases. This is the distortion or buckling of the great vessels, leading to cardiac embarrassment, mentioned before with regard to fibrous contraction. Although such a cause is difficult to prove pathologically, it seems from the evidence in many patients that it has been the cause of the distress; and even death is a possibility when the distortion is extreme.

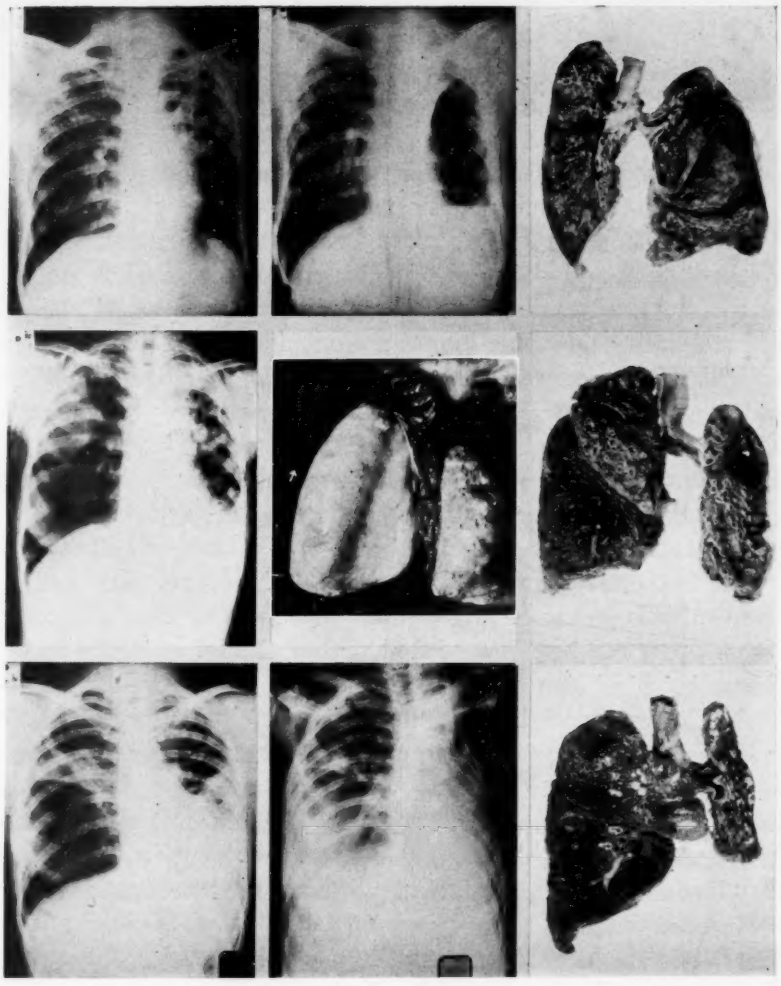
In thoracoplasty the pathological changes depend upon many factors. The most important are those of the lesion itself, when there is or should be a complete compression of the tuberculous lung, including tubercles, infiltrates, and cavities. The circulation is practically all cut off, the lesions become compressed, and there is immediately an appearance of the phenomena of healing. The caseous material begins to dry, reticulum and fibroblasts begin to form, calcification begins, cavity-walls approximate each other, and the whole involvement tends to progress to a fibrous and fibrocalcareous mass. (Plate 2, figures 1 & 2.) Usually, within three months there is a regeneration of bone along the old periosteal beds until a grid-like mass of bone is formed that holds the diseased lung into place and helps to keep the compression.

The complications of thoracoplasty are variable and depend upon the age and type of patient, and the completeness of the operation.

In the early days of the operation, the collapse was sometimes incomplete and the disease extended to the other lung and other parts of the body; amyloidosis occasionally occurs; thrombosis of the pulmonary artery is prone to appear in people past fifty years of age; and sometimes there is dyspnoea from a loss of too much lung tissue.

Plates 2 and 4, figures 7, 8 and 9, show examples of complications in thoracoplasty.

Fig. 1 Fig. 2 Fig. 3



Figs. 4 & 5 Fig. 6

Fig. 7 Fig. 8 Fig. 9

PLATE 4

Fig. 1. Roentgenogram of patient J. H., taken August 31, 1932. Note the large cavity.

Fig. 2. Roentgenogram after pneumothorax and rupture of the cavity into the pleural cavity.

Fig. 3. Gross photograph of a midsection of the lung, revealing the large cavity opening into the pleura, with the collapsed lower lobe against the mediastinum.

Fig. 4. Roentgenogram of patient M. S., showing almost complete destruction of lung on the left side, with a large triangular shadow on the right that was thought to be encysted fluid. On tapping no fluid was obtained, but the patient died of dyspnoea within six hours.

Fig. 5. A photograph of lung being filled with water, showing a needle puncture on the right lower lobe—the only good lobe left. A small triangular flap caused a valvular pneumothorax.

Fig. 6. A gross picture of the midsection, showing the triangular shadow to be a beginning caseous pneumonia.

Fig. 7. Roentgenogram of patient A. S., revealing advanced disease on the left, with involvement of the base of the right upper.

Fig. 8. The same, after thoracoplasty.

Fig. 9. A section through the lung revealing the collapsed lung on the operated side, with healing lesion in the middle and right upper. In the right lower is an abscess resulting from a thrombosis of the pulmonary artery, leading ultimately to death.

Naturally there are other complications accompanying this operation that are inherent in all tuberculosis patients.

In phrenic-nerve surgery there are many interesting results, depending upon the extent and duration of the paralysis. Complete paralysis usually causes a relaxation of the diaphragm and a rise of 7 to 12 cm. immediately after the operation, and producing about 35 per cent collapse. This becomes greater as atrophy develops. Stanbury (17) has recently shown that the muscles gradually atrophy until sometimes only a thin connective-tissue layer is left. This thin layer offers little resistance or none at all to any intrathoracic pressure. So there is a secondary rise of the diaphragm, pulling the stomach or liver upward as time goes on. Left-sided phrenics have been blamed for much stomach distress, due to the reverse action on peristalsis of the right side in respiration. As this is purely a clinical phenomenon, there are no landmarks left by which it can be demonstrated pathologically.

The pathological changes following scaleniotomy, so well worked out by Gale (18), have not been studied, due principally to the fact that they have not been performed in our institution and consequently we have had no material to study.

The lung changes, however, should not be different than those of other forms of collapse, except that the greatest effect should be at the apex. The associated pathological process would be confined to the field of operation.

Compression of lungs by means of foreign substances has been recommended by several authors and has been done in our institution on a limited scale. It may be external to the pleura or within the pleural cavity. It is used to collapse large cavities at the apex. There is frequently a violent reaction following the packing of substances like paraffin into the tissues outside the parietal pleura. Some small fragments of paraffin are frequently dispersed around the edge of the mass into the surrounding tissues, and a foreign-body inflammation results. We have had no opportunity to study the changes produced by other substances, such as rubber bags.

Pneumolysis, or collapse of the lung by loosening adhesions, produces no new pathological changes. There is usually a collapse of the cavities beneath the adhesions, and a shrinking of the stumps of the adhesions themselves. The complications of this operation are most commonly haemorrhage, due to the severing of a large vessel in the adhesion, or

empyema set up by the cutting of lung tissue commonly impaled in the adhesion.

Finally, the collapse produced by liquids within the pleural cavity is sometimes a valuable procedure. The use of oils to prevent adhesions is useful. There is a reaction to some oils that is more violent than even the paraffin packing, mentioned before. Others are quite inert and useful. The results are variable, depending on the conditions before instillation.

Poppy-seed oil has been recommended. Olive oil is used in this institution. Saley and Willis (19) have made thorough studies of various oils experimentally. In the patient that came to autopsy in our institution, the oil was found packed in globules between the pleural layers, with an organizing fibrinous exudate dividing off the globules. It had apparently helped to sterilize the fluid, but did not prevent adhesions.

SUMMARY

A report has been made of the healing factors in pulmonary tuberculosis, particularly those resulting from various forms of medical and surgical treatment. Mention has been made of the mechanism of spontaneous healing, including the walling-off of tubercles on the one hand, and the closure of cavities on the other. The healing following rest-treatment has also been described, including the various sequella, such as emphysema, atelectasis and bronchiectasis. The healing following specific therapy has been discussed, and the healing brought about by the use of gold (sanocrysin) treatment, has been described. In the first draft only there appears to be an increase of physiological activity around the tubercle, with a subsequent accumulation of subacute and chronic inflammatory tissue, and with a marked increase in the bed of the capillaries surrounding the tubercles. Various forms of collapse therapy have also been studied, and illustrations of the various types given. The relative degree of healing is shown when pneumothorax and rest-treatment proceed, side by side. In the former, closure of a large cavity resulted in a year's time; whereas in the latter the cavity did not close within four years. In thoracoplasty, the changes of healing have been studied extensively, and it has been found that cavities are squeezed together, and the circulation of the tubercles shut off, with a resulting penetration of the tissue by reticular fibres, followed by fibrous tissue. The healing following other forms of cavities is also discussed.

REFERENCES

(1) KRAUSE, A. K.: Amer. Rev. Tuberc., 1920–1921, iv, 713.
(2) KRAUSE, A. K.: Environment and resistance in tuberculosis, Harvey Lectures, 1923.
(3) DUNHAM, K.: Radiology, 1933, xxi, 207.
(4) FLETCHER, E.: Tubercle, 1932, xiv, 3.
(5) CORYLLOS, P. N.: Amer. Rev. Tuberc., 1933, xxviii, 1.
(6) CORYLLOS, P. N.: Jour. Am. Med. Assoc., 1933, c, 480.
(7) CORYLLOS, P. N., AND BIRNBAUM, G. L.: Amer. J. Roentgenol., 1929, xxii, 401.
(8) LICHTHEIM, L.: Arch. f. exper. Path. u. Pharmakol., 1875–79, x, 54.
(9) SEWALL, H.: Amer. Rev. Tuberc., 1920–1921, iv, 811.
(10) HENRICHSEN, K. J., FREMMEL, I. F., AND SWEANY, H. C.: Tr. Nat. Tuberc. Assoc., 1927, 203.
(11) HENRICHSEN, K. J., AND SWEANY, H. C.: Amer. Rev. Tuberc., 1933, Supplement, vol. xxviii.
(12) CALMETTE, A., BOGUET, A., AND NEGRÉ, L.: Rev. Tuberc., 1926, vii, 169.
(13) WATANABE, Y., AND SATO, S.: Japan. Report Sanocrysin Research Com., 1927.
(14) LEVINSON, S. A., PETERSEN, W. F., AND MILLER, G.: Amer. Rev. Tuberc., 1927, xvi, 285.
(15) JOBLING, J. W., AND PETERSEN, W. F.: Jour. Am. Med. Assoc., 1914, lxiii, 1930.
(16) PASTEUR, W.: Brit. J. Surg., 1914, i, 589.
(17) STANBURY, W. S.: Amer. Rev. Tuberc., 1934, xxix, 528.
(18) GALE, J. W., AND MIDDLETON, W. S.: Arch. Surg., 1931, xxiii, 1.
(19) SALEY, D. H., WILLIS, H. S., AND ELLWART, L.: Tr. Nat. Tuberc. Assoc., 1934.

THE CULTIVATION OF TUBERCLE BACILLI FROM THE BLOOD OF TUBERCULOUS PERSONS[1]

MORRIS SIEGEL AND BELLA SINGER

The search for tubercle bacilli in the blood has attracted many investigators, because disseminated tuberculous lesions are very frequently seen in tuberculous persons. Even before the tubercle bacillus was discovered, Villemin, in 1868, had shown by his inoculations of rabbits that the causative agent of tuberculosis "virus" can be present in the blood-stream. After Koch's discovery in 1882, many have essayed to detect tubercle bacilli in the blood. At first, tubercle bacilli were found in the stained smears of postmortem blood clots (Weichselbaum). In living tuberculous persons, the smear of a drop of blood was tried (Liebman). In 1908, Stäubli used the sediment of blood haemolyzed with 3 per cent acetic acid in his search for tubercle bacilli in the blood. In the next year, Schnitter used antiformin on the sediment of blood haemolyzed with acetic acid. This procedure, called the Stäubli-Schnitter method, became popular in the search for tubercle bacilli. In 1909–1912, Liebermeister, Rosenberger, Kurashige and others stimulated universal research and discussion by reporting almost 100 per cent positive results in smears of sediments of blood from tuberculous persons. Liebermeister also had positive blood-smears in patients with rheumatic fever, and Kurashige in apparently normal patients. Other investigators had only a few or no postitive results in tuberculous patients (Fraenken; Lange and Lindemann) and negative results in nontuberculous patients. It was admitted by most authors that the smear alone was unreliable because many artefacts, such as poorly decolorized smears, fibrin shreds, fuchsin crystals and scratches on the slide might be mistaken for tubercle bacilli. It was also admitted that many strains of acid-fast bacilli were present in plants and animals (M. Rabinowitsch), in the air and water, even in distilled water (Brem), which could not be differentiated by smear from the tubercle bacilli.

Guinea-pig inoculations of whole blood were also tried, but the undoubted positive results were few. Kahn, in 1913, was able to collect

[1] From the Pediatrics Service of Doctor Bela Schick, Sea View Hospital, New York City

from the literature 32 out of 512 tuberculous cases, in which the results of guinea-pig inoculation could be accepted as positive.

Blood cultures for detecting tubercle bacilli in the blood-stream were even more unsatisfactory. Of 558 tuberculous cases reported from various sources from 1906 (M. Rabinowitsch) to 1929, Wilson was able to collect only 6 instances (about 1 per cent) in which tubercle bacilli were undoubtedly cultured from the blood of living persons.

From clinical, experimental and pathological experience, it has been felt that the bacilli are more often present in the blood-stream of tuberculous persons than blood culture and guinea-pig inoculation were able to demonstrate. Clinically, evidence of disseminated tuberculosis is frequently seen, especially in infants. Experimentally, vascular dissemination can be demonstrated while the primary lesion is developing. Pathologically, disseminated lesions are seen in almost every person that dies of tuberculosis.

In 1930, Loewenstein reported that the tubercle bacilli can be regularly detected in the blood of active tuberculous persons by his culture method.[2] He has also reported many positive blood cultures from the blood of persons with other diseases than tuberculosis, such as acute polyarthritis, chronic polyarthritis, chorea, retrobulbar neuritis, multiple sclerosis, and dementia praecox. Many workers have tried to duplicate his work. In tuberculous cases, their results have not exceeded those obtained by guinea-pig inoculation or blood culture before Loewenstein's reports in 1930. In nontuberculous cases, the results, except in rare instances, have been uniformly negative.

In 1931, Shapiro, working in the laboratory of Sea View Hospital, reported negative cultures in 33 blood specimens from children with rheumatic fever, chorea, and erythema nodosum, and "7 macroscopic positive cultures" from 162 blood specimens from tuberculous patients. In spite of these few positive results, and in spite of the failure of many other workers to verify Loewenstein's unusual results, we undertook a similar study. We did this enthusiastically, because clinical evidence

[2] The Loewenstein method consists of culturing the sediment of citrated blood, free from haemoglobin, on the surface of coagulated egg medium containing congo-red, asparagin, glycerine and salts of dipotassium phosphate, magnesium sulphate and sodium citrate. Loewenstein calls the cultures positive if colonies resembling growths of tubercle bacilli are visible on the medium (macroscopic positive), or if the smear of the surface of the medium which has no visible growth after two months' incubation at 38°C. contains acid-fast bacilli upon microscopic examination (microscopic positive).

of vascular dissemination of the tubercle bacilli was seen so often in our patients that many positive blood cultures were expected.

METHOD

The Loewenstein technique was employed in a series of 911 blood specimens taken from 422 tuberculous patients, from January, 1933, to June, 1934. The work may be divided into 3 groups. From January to May, 1933, 3 per cent acetic acid was used to haemolyze the blood and 1 cc. of sulphuric acid (15 per cent by volume) was employed to destroy associated contaminants (group 1). From July, 1933, to March, 1934, distilled water was used as the haemolytic agent, followed by 0.5 cc. of sulphuric acid (15 per cent by volume) (group 2). From April to June, 1934, the blood was haemolyzed with distilled water but no sulphuric acid was used (group 3).

In most instances, 2 to 10 cc. of blood were mixed with 2 to 3 cc. of sterile 10 per cent sodium citrate in centrifuge tubes of 50-cc. volume and well shaken to prevent clotting. In the group from April to June, 1934 (group 3), 4 to 14 cc. of blood were collected and divided into two approximately equal parts. One-half was cultured according to the Loewenstein technique. The other half was mixed with 0.4 cc. of 10 per cent sodium citrate and directly cultured without removing the haemoglobin, on Bordet-Gengou and Loewenstein media in petri dishes (Mishulow).

The details of our method closely followed those advised by Loewenstein. In the first group, when the haemoglobin was to be removed with acetic acid, the citrated blood was first centrifugated for 20 minutes at 2,000 *r.p.m.* The supernatant fluid was decanted and 3 per cent acetic acid was added until the blood sediment was completely haemolyzed. The mixture was centrifugated for 20 minutes, the supernatant fluid was decanted and the sediment was treated with 1 cc. of 15 per cent sulphuric acid for one minute. Then 40 cc. of distilled water were added and the mixture was again centrifugated for 20 minutes. After another washing with 40 cc. of distilled water, the sediment was inoculated on the surface of 6 tubes of Loewenstein congo-red medium.

With the sterile distilled water as the haemolytic agent (second and third groups), the citrated blood was mixed with 30 cc. of distilled water; and the contents were well shaken and centrifugated for 20 minutes. The supernatant fluid was decanted; the sediment was well shaken and

again washed with 30 to 40 cc. of distilled water. The small grayish sediment that remained was thoroughly broken up with a pipette (2 mm.-bore) and inoculated on the surface of 3 or 4 tubes of Loewenstein congo-red medium (group 3). When sulphuric acid was used (group 2), 0.5 cc. of 15 per cent by volume was added to the sediment free from haemoglobin, and the contents well shaken for one minute. About 40 cc. of distilled water were added and the mixture was centrifugated for 20 minutes. The sediment was again washed with 40 cc. of distilled water. The minute whitish sediment that remained was thoroughly broken up with a pipette and spread over the surface of 3 or 4 tubes of Loewenstein medium.

In all instances, the tubes were completely sealed at once with sealing-wax, and allowed to lie horizontally for 24 hours with the inoculum evenly distributed over the entire surface. Then they were placed upright in the incubator at 38°C., and were examined at weekly intervals for colonies of tubercle bacilli (macroscopic positive culture). If no growth was visible after 2 months, a smear was made of the edges, bottom and surface of the medium and examined under the microscope for tubercle bacilli (microscopic positive culture). If the results of the microscopic examination were negative, the surface of the media was scraped into 1 cc. of sterile distilled water and then washed with an additional 2 cc. This was centrifugated for 30 minutes and the sediment again examined by smear. In all microscopic examinations, the Ziehl-Neelsen method of staining was used and the whole surface of the smear was examined by means of a mechanical stage.

RESULTS

In the entire series of 422 tuberculous cases (911 specimens) in which the Loewenstein technique was employed there were 6 (1.4 per cent) "macroscopic positive" cultures. These were all grayish-white, coarse colonies, typical of tubercle bacilli, with characteristic growth on subcultures. On subcutaneous inoculation of guinea pigs, local caseous lesions, caseous regional lymph nodes and generalized miliary tuberculosis were produced. In 12 other instances, chromogenic saprophytic colonies of acid-fast bacilli were isolated.

There were 55 (13.0 per cent) "microscopic positive" cultures in which one or more clusters of acid-fast rods, resembling tubercle bacilli, were seen on the smears. There were no macroscopic growths in these cases. In no instance was subculture or animal inoculation positive, so that

all 55 primary cultures are considered as doubtful positive results. Forty-three (10.1 per cent) additional cultures in which smears showed only a few isolated acid-fast rods were considered as negative and were not included in the "microscopic positive" results.

Acetic acid, as a haemolytic agent, was used on 150 specimens from 98 cases (group 1). Of these, there were 3 macroscopic undoubted positive cultures and 10 microscopic positive cultures (table 1). Of the 3 macroscopic cultures, one was from umbilical blood obtained from the newborn of a tuberculous mother whose placenta had a caseous tuber

TABLE 1

Results obtained in detecting tubercle bacilli in the blood-stream of tuberculous persons

Group 1: Loewenstein's method—acetic acid and sulphuric acid

TYPE OF CASE	NUMBER OF CASES	SPECIMENS	RESULTS		
			Negative	Macroscopic Positive	Microscopic Positive
Adults. Pulmonary tuberculosis—all stages (majority advanced)	57	71	63	1	7
Children:					
Advanced pulmonary	18	47	44	0	3
Pneumothorax	10	18	18	0	0
Thoracoplasty	1	2	2	0	0
Umbilical blood of newborn of tuberculous mothers	7	7	6	1	0
Postmortem blood:					
Of newborn of tuberculous mothers	4	4	3	1	0
Of adult who died of tuberculosis	1	1	1	0	0
Total	98	150	137	3 (3.0%)	10 (10.0%)

culous area, 2 cm. in diameter; another was from the postmortem blood of this newborn, who died in 3 hours with no evidence of tuberculous lesions; the third was from an adult with advanced pulmonary tuberculosis. The 10 microscopic positive cultures were from children and adults with pulmonary tuberculosis.

There were 6 negative specimens of umbilical blood from the newborn of tuberculous mothers whose placentas had no visible tuberculous lesions. Also negative were specimens of postmortem heart's blood from three of the newborn infants who died soon after birth with no evidence of tuberculosis. In addition, there was a negative culture of postmortem heart's blood from an adult dying of tuberculosis.

Of the 3 "macroscopic positive" cultures in this group, the primary culture from the umbilical blood showed two minute, coarse, grayish-white colonies near the side and bottom of the tube. The postmortem blood, however, of the newborn had numerous coarse, grayish-white colonies over the entire surface. The third macroscopic culture, from the adult with pulmonary tuberculosis, had a scant growth along the side. On subculture, typical colonies of tubercle bacilli were seen. The 10 microscopic positive cultures were negative to subculture.

The result of our blood-culture study in this group was rather disappointing. We felt that perhaps something was wrong with our technique. One of us, therefore, visited Loewenstein's laboratory and worked there for five weeks to learn the details of Loewenstein's method. Loewenstein was an eager and generous host. He observed his visitor to be certain that the details of his method were being correctly followed and even allowed him to share the daily routine blood-culture work with his technician.

We returned to our work at Sea View Hospital with the hope of improving results, although we felt that there was little that could be done to alter our procedure. Instead of acetic acid to haemolyze the blood, sterile distilled water was now employed, as advised by Loewenstein. In addition, sulphuric acid was again used to destroy contaminations in the blood sediment. After nine months' work, there were 44 microscopic positive cultures and only one macroscopic positive culture among 663 specimens from 261 patients, all tuberculous (table 2).

In this second group of our study we investigated the effects of haemoptysis, thoracoplasty, pneumothorax, and surgery in bone tuberculosis. At first the blood specimens of 58 patients with haemoptysis were examined. Of 114 specimens from 58 patients with blood in their sputum, there were only 7 microscopic positive cultures and no macroscopic cultures. The blood of 37 of these patients was examined several days after their haemoptysis had ceased. There were 8 microscopic positive cultures only.

It was then thought that bacillaemia might occur during and immediately after thoracoplasty and bone fusion operations. Blood specimens were taken before, during and after operations. The preoperative specimens were obtained immediately preceding the operation. In several instances, they were also taken days and weeks before the operation. In 10 cases, 1 to 3 specimens were obtained during the operation and 5 to 6 specimens at intervals of $\frac{1}{2}$ to 3 hours after the operation, and at

weekly intervals for 2 to 3 weeks. Of 41 specimens from 29 patients before thoracoplasty operation, there was only one microscopic positive culture. Of 200 blood specimens obtained during and after operation, there were

TABLE 2

Results obtained in detecting tubercle bacilli in the blood-stream of tuberculous persons

Group 2: Loewenstein's method—distilled water and sulphuric acid

TYPE OF CASE	NUMBER OF CASES	SPECIMENS	RESULTS		
			Negative	Macroscopic Positive	Microscopic Positive
Adults:					
With haemoptysis	58				
During haemoptysis	58	114	107	0	7
After haemoptysis	37	37	29	0	8
Thoracoplasty	29				
Preoperative		41	40	0	1
Postoperative		200	183	1	16
Pneumothorax	10				
Before refill		21	21	0	0
After refill		31	29	0	2
Orthopaedic operations	7				
Preoperative		20	20	0	0
Postoperative		21	21	0	0
During pregnancy	9				
Before delivery		9	9	0	0
After delivery		13	13	0	0
Others—majority with advanced pulmonary tuberculosis or critically ill	118	120	112	0	8
Children:					
Active pulmonary	5	9	8	0	1
Inactive pulmonary	15	15	15	0	0
Umbilical blood of newborn of tuberculous mothers	6	6	5	0	1
Postmortem blood:					
Of newborn of tuberculous mothers	2	4	4	0	0
Of children who died of tuberculosis	2	2	2	0	0
Total	261	663	618	1 (0.4%)	44 (16.9%)

16 microscopic positive cultures and one macroscopic positive culture. Twelve of the 16 postoperative microscopic positives were in specimens taken 2 to 15 days after operation, while four of the specimens were taken within one hour after the operation. The one macroscopic posi-

tive culture was from a blood specimen taken immediately after a first-stage thoracoplasty in which the postoperative course was uneventful. The patient also had artificial pneumothorax on the contralateral side. The immediate postoperative course in all the patients was good except for one patient who developed empyema.

The effect of collapse of the lung by pneumothorax in the production of a bacillaemia was studied in 10 patients. Blood specimens were taken immediately before and after the administration of 300 to 400 cc. of air into the pleural cavity. All of the 21 specimens before pneumothorax were negative. After the administration of air, there were 2 microscopic positive cultures in 31 specimens.

In 15 preoperative cases with bone-and-joint tuberculosis, there was only one microscopic positive culture out of 35 blood specimens. In 7 of these cases, 21 blood specimens taken during and after operation for bone tuberculosis were negative. The postoperative course in all 7 cases was good. There was no clinical evidence of recent tuberculous bacillaemia in any of the cases.

In addition, there were 8 microscopic positive cultures among 118 specimens from adults critically ill with tuberculosis; one microscopic positive culture in 24 specimens from children with active or inactive pulmonary tuberculosis; and one microscopic positive culture in 6 umbilical blood samples from newborn children of tuberculous mothers. Postmortem blood specimens from two of the newborn with no evidence of tuberculosis, and from 2 children who died of tuberculosis were negative.

In groups 1 and 2 combined, of 813 blood specimens from 359 persons with tuberculosis, there were 4 (1.1 per cent) macroscopic positive and 54 (15.0 per cent) microscopic positive blood cultures. The results, although comparable to those obtained by other workers, such as Saenz and Popper, were not encouraging. It was still felt that tubercle bacilli should be more frequently detected in the blood-stream of living tuberculous patients than we were able to obtain by the Loewenstein method. Popper, in 1933, after 3 years' trial of the Loewenstein method in over 1000 cultures, finally modified it[3] with better results. Saenz, after 4

[3] Popper allows the blood specimen to remain at 38°C. in a fluid nutrient medium of 2 per cent glycerine, 0.5 per cent asparagin, salts of sodium citrate, magnesium phosphate, mono-potassium phosphate, di-sodium phosphate, with 0.5 per cent saponin to haemolyze the blood. At the end of 10 days, this is centrifugated, and the sediment inoculated on the surface of Loewenstein's medium. The cultures are kept in the incubator at 38°C. for two months.

years' trial, has decided that the subcutaneous inoculation of whole blood into guinea pigs gave better results than the Loewenstein method. Several workers (Abt, Mishulow; Saenz) found that haemoglobin did not inhibit the growth of tubercle bacilli in the blood-stream; and that the tubercle bacilli grew readily when whole blood was directly inoculated on the surface of the medium. Mishulow and Park found that the

TABLE 3

Results obtained in detecting tubercle bacilli in the blood-stream of tuberculous persons

DIAGNOSIS	GROUP 3		LOEWENSTEIN METHOD DISTILLED WATER			WHOLE-BLOOD CULTURE METHOD ON BORDET-GENGOU AND LOEWENSTEIN MEDIA (MISHULOW)	
	Number of Cases	Number of Specimens	Negative	Macroscopic Positive	Microscopic Positive	Negative	Macroscopic Positive
Adults:							
Advanced or critical pulmonary tuberculosis	28	33	33	0	0	32	1
Pulmonary & bone tuberculosis	10	14	14	0	0	14	0
Children:							
Advanced or critical pulmonary tuberculosis	17	34	32	2	0	32	2
Pneumothorax	1	2	1	0	1	2	0
Pulmonary & bone tuberculosis	1	1	1	0	0	1	0
Tuberculous pregnant women:	1						
Before delivery		1	1	0	0	1	0
After delivery		4	4	0	0	4	0
Orthopaedic cases:							
Pre and Postoperative	4	8	8	0	0	8	0
Postoperative	1	1	1	0	0	1	0
Total	63	98	95	2	1	95	3
Percentage of positive cases				3.2	1.6		4.8

human tubercle bacilli in the whole blood of experimentally infected animals grew freely on Bordet-Gengou medium composed of 30 per cent horse-blood. Since their method was less time-consuming and the results excellent in the culture of animal blood, it was decided to compare it with Loewenstein's method when human blood was used. There were 98 blood specimens from 63 tuberculous patients (group 3), most of whom were critically ill with advanced pulmonary tuberculosis and

had clinical evidence of tuberculous bacillaemia. In particular, the blood of several infants with miliary tuberculosis was repeatedly cultured (table 3).

The details of this comparative study have been published (Mishulow, *et al.*). Briefly, about 4 to 14 cc. of blood were withdrawn and divided into two approximately equal parts. One-half was cultured according to the Loewenstein technique. Sterile distilled water served as the haemolytic agent, and no sulphuric acid was used. The other half of the blood specimen was mixed with 0.4 cc. of 10 per cent sodium citrate and cultured by Mishulow on the surface of Bordet-Gengou and Loewenstein media in 6 to 10 petri plates. In each plate about 0.5 cc. of citrated blood was evenly distributed over the whole surface of the medium and thus cultured without the preliminary removal of haemoglobin.

By the whole-blood method there were 3 macroscopic positive cultures as compared with 2 macroscopic and one microscopic positive culture by the Loewenstein technique. The macroscopic growths were scant and present in only one of 4 tubes of medium on which the blood sediment had been cultured by the Loewenstein method. By the whole-blood method, there was a single colony in each of two positive blood cultures, one on the Bordet-Gengou medium and the other on the Loewenstein medium. The third positive culture by the whole-blood method had two colonies on a plate of Bordet-Gengou medium and one colony on a plate of Loewenstein medium. The microscopic positive culture by the Loewenstein method consisted of several small clumps of acid-fast bacilli, resembling tubercle bacilli, in the smear of the surface of inoculated medium in one tube only. Four other tubes of medium inoculated with the same specimen were negative. This microscopic positive culture was considered as a doubtful positive, because its subculture and animal inoculations were negative.

In no instance were both portions of a divided specimen of blood positive by both methods. However, by repeating the blood cultures at weekly intervals, two infants, 9 and 10 months old, with miliary tuberculosis, were positive by both methods. A third case was macroscopically positive by the whole-blood culture method only. The blood was taken from an adult, 46 years old, critically ill with pulmonary tuberculosis. No other specimens were cultured in this case. The fourth case was microscopically positive by the Loewenstein method. The blood specimen was taken from a girl, 13 years of age, with advanced

pulmonary tuberculosis. In this case a second specimen of 11 cc. was negative.

All of 24 specimens obtained from 16 persons with pulmonary and bone tuberculosis gave negative results by both methods. In 5 cases, blood specimens taken soon after operations for bone tuberculosis were also negative by both methods. Of these 5 cases, 3 had tuberculosis of the spine, one of the knee, and one of the shoulder.

In this group of 98 blood specimens from 63 tuberculous persons, haemoglobin did not seem to inhibit the growth of tubercle bacilli. If one combines the results of the Loewenstein method in the 63 cases (group 3) with the results of his method in groups 1 and 2, one has a total of 6 (1.4 per cent) macroscopic and 55 (13 per cent) microscopic positive cultures from 422 tuberculous persons.

SUMMARY

1. The Loewenstein method of culturing tubercle bacilli from the blood was employed in 911 blood specimens from 422 tuberculous persons. There were 6 (1.4 per cent) macroscopic positive cultures and 55 (13.0 per cent) microscopic positive cultures.

2. The macroscopic positive cultures were undoubted cultures of tubercle bacilli according to subculture and virulence tests. The microscopic positive cultures were not definitely proved to be cultures of tubercle bacilli, since subcultures and animal inoculations gave negative results.

3. The primary macroscopic growths of tubercle bacilli from the blood of living tuberculous persons were scant, usually only one or two colonies appearing from a sample of 5 to 10 cc. of blood.

4. The 6 macroscopic positive cultures were obtained from the following: two infants with miliary tuberculosis, an adult critically ill with pulmonary and intestinal tuberculosis, an adult immediately after a first-stage thoracoplasty operation, the umbilical blood of a tuberculous placenta, and the postmortem heart's blood of a newborn who died 3 hours after birth with no evidence of tuberculous lesions.

5. Haemoglobin did not seem to inhibit the growth of tubercle bacilli according to a comparative study of the Loewenstein method and the "whole-blood" method. In this series of 98 specimens from 63 tuberculous persons, there were 3 macroscopic positive cultures by the direct culture of whole citrated blood as compared with 2 macroscopic positive cultures and 1 microscopic positive culture by the use of Loewenstein's method.

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BIBLIOGRAPHY

ABT, F.: Schweiz. med. Wchnschr., 1931, lxi (xii), 1084.
BREM, W.: Jour. Am. Med. Ass., 1909, liii, 909.
FRAENKEN, C.: J. State Med., 1912, xx, 722.
KAHN, E.: Beitr. Klin. Tuberk., 1913, xxviii, 283.
KURASHIGE, T.: Ztschr. Tuberk., 1911, xvii, 347.
LANGE AND LINDEMANN: Centralbl. Bakt., ref., 1913, lvii, 285.
LIEBERMEISTER, G.: Med. Klin., 1912, viii, 1018.
Virchow's Arch. path. Anat., 1909, cxcvii, 332.
LIEBMAN, V.: Berl. klin. Wchnschr., 1891, xxviii, 97, 393.
MISHULOW AND PARK: J. Prev. Med., 1932, vi, 95.
MISHULOW, SIEGEL, SINGER, MELMAN AND ROMANO: J. Lab. & Clin. Med., 1935, xx, 1063.
POPPER, BODART AND SCHINDLER: Virchow's Arch. path. Anat., 1932, cclxxxvi, 615.
POPPER, H.: Klin. Wchnschr., 1933, xii, 1650.
RABINOWITSCH, M.: Ztschr. Tuberk., 1906, ix, 305.
ROSENBERGER, R.: Am. J. M. Sc., 1909, cxxxvii, 267.
SAENZ, A.: Ann. l'Inst. Pasteur, Paris, 1934, lii, 645.
SAENZ, PASCAL, COSTIL AND CHAPOULAUD: Comp. Rend. Soc. Biol., 1934, cxv, 1681.
SCHNITTER: Deutsche med. Wchnschr., 1909, xxxv, 1566.
SHAPIRO, L.: Amer. Rev. Tuberc., 1932, xxvi, 418.
STÄUBLI: München. med. Wchnschr., 1908, lv, 2601.
VILLEMIN, J. A.: Études sur la tuberculose, Paris, 1868.
WEICHSELBAUM, A.: Wien. med. Wchnschr., 1884, xxxiv, 332, 365.
WILSON, G. S.: Tuberculous bacillemia, London, 1933.

TUBERCULOUS BACILLAEMIA

Experimental Studies with the Three Pathogenic Types of Tubercle Bacilli

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The study of tuberculous bacillaemia is important for obtaining a true picture of the nature of tuberculosis. It is only natural that, with the perfection of details of technique and the elucidation of accidental errors as well as quantitative interpretation, many of the older findings and conceptions will either be verified, or modified or abandoned. At times there may even be advantages to startling theories, based on errors, in that they stimulate exhaustive studies along certain important lines. They also show that many an error originating from the investigator's laboratory must be returned there from the clinic for ultimate solution and explanation under better-controlled conditions. There is no more striking example of this than the exhaustive recent accumulation of literature on tuberculous bacillaemia (1), and the simple explanation of the possible errors resembling those which occurred on the same subject earlier (2). In previous reports (3) (4) we pointed out that, although Loewenstein's medium for the determination of tubercle bacilli in the blood could be considered suitable medium for growing small numbers of tubercle bacilli, the use of acetic acid in the preliminary treatment of the blood was injurious to tubercle bacilli, while it permitted acid-fast saprophytes to survive and confuse the ultimate culture findings. Since then, Saenz (5) has pointed out that an important source of error was that many investigators, in announcing positive results with blood taken from patients with diseases heretofore considered as bearing no aetiologic relationship with tuberculosis, based their reports on finding microscopic colonies after scraping the surface of the medium when no macroscopic growth was present. Such colonies contain acid-fast bacilli, but are only groups of dead bacilli, which can be found in rubber tubing or in the various solutions that have been employed in preparing the culture medium or stains.

In 1933, Wilson (6) exhaustively reviewed the subject of tuberculous bacillaemia. He pointed out that much of the published work rested

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upon fallacies and was to be discounted: that similar criticisms might apply to other work on tuberculous infections, including at least part of that dealing with filterable forms of tubercle bacilli; that there were reasons for concluding that it is impossible to identify tubercle bacilli in the blood by direct microscopical examination, while, on the other hand, the animal-inoculation method, in capable and experienced hands, is the most reliable means of demonstrating virulent tubercle bacilli. He went on to say that only a small number of positive results had been obtained by this method, most of them having been with blood from patients suffering from miliary tuberculosis, tuberculous meningitis, advanced pulmonary tuberculosis, and, occasionally, surgical tuberculosis. It may be concluded, according to Wilson, that tuberculous bacillaemia, except as a sporadic phenomenon, is uncommon except in patients suffering from advanced and progressive disease.

In *Appendix B* of the same report, Schwabacher reviewed the literature and recorded scattered data on guinea pigs and rabbits from the intramuscular injection of relatively large amounts (0.1 to 1.0 mgm.) of tubercle bacilli. However, the method of drawing the blood from the heart (7), inasmuch as many of the animals had advanced generalized disease and Loewenstein's acetic-acid method was used for isolation, was open to criticism. Rabbits, on the other hand, from whose ears blood was examined, rarely proved positive. When intravenous injections were given, even large amounts of bacilli (0.01 to 10 mgm.) disappeared from the blood rapidly. However, the general conclusion drawn was that there is a fairly efficient clearing mechanism operative in the animal body, tending to free the circulating blood of organisms that have gained access to it from tuberculous lesions in tissues; that tubercle bacilli do not multiply in the blood-stream itself; and that bacillaemia, except as a transitory phenomenon, is not likely to occur previous to advanced stages of an actively progressing disease. In 1912, Alfred Hess(8) made some interesting observations on the results of rabbit inoculations. He investigated whether the bovine bacillus of relatively high virulence for these animals and the human type of low virulence, when given intravenously, persisted in the blood-stream approximately the same length of time. For this purpose, 0.01 and 1 mgm. of culture were given intravenously, and guinea pigs were used to test the presence of the bacilli in citrated blood. Although there was some irregularity in the guinea-pig results, it appeared that the more virulent bovine bacilli remained in the circulation longer than did human tubercle bacilli. An

avirulent strain of bovine bacilli for rabbits also disappeared more rapidly than the virulent bovine strain from the circulation. Hess noted also the return of the bacilli to the blood-stream after an intervening period of absence in the course of progressive tuberculosis.

That many factors may play their part in the rate of removal of micro-organisms from the circulation is indicated by the recent observations of Rheingold (9). He found that large doses of *B. prodigiosus* injected into the blood-stream of dogs disappeared at a very rapid rate for about thirty minutes, and, after this interval, at a much slower rate. The organisms accumulated only in those organs which contained reticulo-endothelial cells; and the chief agent of destruction was phagocytosis by these cells. Dogs fed protein, carbohydrate, or fat always showed a greater rate of decrease than starved ones. Dogs fed agar reacted in the same way as starved animals.

These observations indicate the importance of quantitative evaluation. In an earlier communication, it was shown that accurate colony-counts of blood containing tubercle bacilli could only be crudely utilized when planting this blood directly on culture mediums (10). This detrimental inhibitory effect of fresh or citrated blood was obviated by sulphuric-acid treatment and subsequent neutralization, but, in spite of this precaution, an accurate colony count was still not feasible. It was also shown that, when properly performed, culture tests were as capable of yielding positive results from tissue and blood as guinea-pig tests, each being a delicate method for showing small numbers of human and bovine tubercle bacilli (11). The culture method is to be preferred for avian tubercle bacilli, since these grow well on certain good media (12) (13), to the point, indeed, of dilution extinction in fine suspensions.

Plan of Experiment

Our plan of experiment was to determine, if possible, the significance of tuberculous bacillaemia in susceptible animals, and to learn, also, whether virulence for a particular species played a part in the persistence of the tubercle bacilli in the circulation. A highly virulent strain of each of the three pathogenic varieties,—human, bovine, and avian,—was chosen. We selected the guinea pig, susceptible to the human and bovine, but not to the avian bacilli; the rabbit, susceptible to the bovine and avian, but not to the human bacilli; the chicken, susceptible only to the avian; and the dog, susceptible to the human and bovine bacilli (though not markedly so), but not to the avian bacilli. It seemed that these tests should give a

good cross-section of any bacillaemic tuberculosis in animals, and throw light on the condition in human beings. However, in order to make the observations more complete, one group of animals of each species received heavy intravenous injections (1.0 mgm. of fine suspension); another group, moderate dosages (0.001 mgm. of fine suspension); and a third group, relatively small doses (0.000,001 mgm. of fine suspension). All the cultures used for inoculation were taken from the surface of a good medium and were, when removed for use, of about the same age, three to four weeks old and actively growing at 37.5°C. Every precaution was taken to prevent contamination of the blood from outside sources or during the taking of the sample for test. The samples were usually obtained from the ear and never near the site of previous intravenous injection of bacilli. All positive cultures were verified bacteriologically, to exclude confusion with acid-fast saprophytes.

Method of Test for Tubercle Bacilli in the Blood

The specimen of blood was obtained by means of a sterile syringe containing one-tenth volume of sterile 3 per cent neutral sodium-citrate solution, after thoroughly cleaning the site with a number of applications of equal parts of pure acetone and 95 per cent alcohol following depilation. The specimen, varying from 2 to 20 cc., according to the size of the animal from which blood was obtained, was treated with 2 volumes of 6 per cent sulphuric acid and incubated at 37°C. with frequent shaking for 45 minutes, after which it was carefully neutralized with an appropriate amount of dilute (4 per cent) sodium hydroxide (cautiously added), using brom-thymol-blue as indicator. It was then washed with sterile 0.9 per cent sodium-chloride solution, and the blood sediment was carefully planted on 4 crystal-violet-potato tubes (14) and 4 inspissated egg-yolk (12) tubes. After preparation of the culture-tubes to maintain water-balance (15) they were incubated at 37°C. for at least three months, if they had not become positive before.

In order to verify the ability to recover the bacilli when present in small numbers after adding them to the various bloods of the different animals, graded amounts of fine suspensions of these bacilli (from 0.001 to 0.000,-000,01 mgm.) were added to the blood of the guinea pig, rabbit, chicken and dog, and these bloods were then submitted to culture by the method described above, with results as recorded in table 1.

In analyzing table 1, it must be remembered that, when using suspensions prepared for tests of this type, a positive result with 0.000,000,01

mgm. suspension is about the point of maximum dilution for human and bovine bacilli that will still grow, although, for avian bacilli, suspensions to 0.000,000,001-mgm. dilution still grow consistently on a good medium. The results in table 1 therefore indicate that tubercle bacilli, contained in blood in small numbers, can be recovered with good consistency by the method described.

TABLE 1

The recovery of virulent human, bovine or avian tubercle bacilli from the citrated blood of the guinea pig, rabbit, chicken or dog by means of culture

CITRATED BLOOD USED	AMOUNT OF BACILLI IN MGM. PER CC. PLACED IN THE BLOOD	STRAIN OF VIRULENT BACILLI USED		
		Human Sputum 37	Bovine* Strain 39	Avian Strain 3
Guinea pig	0.001	3†	3	3
	0.000,01	4	3	3
	0.000,000,1	4	3	3
	0.000,000,01	4	3	3
Rabbit	0.001	3	3	3
	0.000,01	3	4	3
	0.000,000,1	4	4	3
	0.000,000,01	4	0	4
Chicken	0.001	4	4	3
	0.000,01	5	5	3
	0.000,000,1	6	5	10
	0.000,000,01	0	6	0
Dog	0.001	3	3	3
	0.000,01	4	3	3
	0.000,000,1	6	8	6
	0.000,000,01	6	0	6

* This bovine strain was non-glycerophilic and had to be grown on mediums without the addition of glycerol.

† The numeral indicates the earliest positive culture in weeks observed on the two mediums (potato and egg) used. 0 indicates a negative result.

Recovery of Tubercle Bacilli from the Blood of Animals Following Intravenous Injection in Varying Amounts

Many of the tests with the various strains and dilutions of tubercle bacilli were run in triplicate, and, although showing slight variations for the blood findings among the individual animals being tested, the positive and negative findings in the various dilutions of the suspensions of the same strain were fairly constant. Therefore, in tabulation, only one

animal was chosen as representative and is recorded under each division. With the guinea pig, especially when blood could not be satisfactorily drawn at daily intervals from one animal, the records are a composite of a number of animals, to fill in the gaps which would otherwise occur in tabulation. Samples of blood from the animals were usually taken

TABLE 2

The presence of tubercle bacilli in the blood of guinea pigs following the intravenous (ear-vein) injection of varying amounts of virulent human, bovine, and avian tubercle bacilli

STRAIN OF BACILLI	AMOUNT INJECTED INTRAVENOUSLY IN MGM.	BLOOD-CULTURE FINDINGS AT VARIOUS INTERVALS (IN DAYS) AFTER INTRAVENOUS INJECTION														POSTMORTEM NOTES
		1 hour	1 day	2	3	4	7	10	14	20	30	40	60	80	100	114	
Human 37	1.0	3*	4	3	3	6	4	3	3	4	4						Died 30 days. Tb. 4†
	0.001	0	0	0	0	0	0	0	0	0	0	0	0	0	0		Killed 114 days. Tb. 4
	0.000,001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 114 days. Tb. 3
Bovine 39	1.0	3	4	3	3	3	4	3									Died 14 days. Gen. acute tb.
	0.001	8	0	0	0	0	0	0	0	0	0						Died 40 days. Tb. 4
	0.000,001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 114 days. Tb. 4
Avian 3	1.0	3	3	3	3	3	4	3	5	6	5	8					Died 42 days§
	0.001	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 114 days. Tb. neg.
	0.000,001	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 114 days. Tb. neg.

* The numerals indicate the earliest period in weeks at which time positive cultures were obtained.

† The amount of tuberculosis found at postmortem is graded from negative, indicating the absence of macroscopic evidence of tuberculosis in any of the organs, to 4, indicating a massive involvement of all the important internal organs including the lungs, liver, and spleen, most of the abdominal and thoracic glands, and a marked massive tuberculous splenomegaly.

§ No gross tubercles. Acute intoxication with splenomegaly.

within one hour of the intravenous injection of the suspension of the bacilli, and afterward at regular intervals starting a day apart; later at bidaily and then at tridaily intervals for at least three to four months, when the active and progressive stages of the disease had usually passed.

From an examination of table 2, it is to be noted that in the guinea

pig the blood only contained tubercle bacilli after the first day following large intravenous injections (1 mgm.), but with the virulent human and bovine bacilli they persisted in the blood until death of the animal, that resulted from the overwhelming intravenous dose. This same large dose of avian bacilli, not particularly pathogenic for the guinea pig by other

TABLE 3

The presence of tubercle bacilli in the blood of rabbits following the intravenous (ear-vein) injection of varying amounts of virulent human, bovine and avian tubercle bacilli

STRAIN OF BACILLI	AMOUNT INJECTED INTRAVENOUSLY IN MGM.	BLOOD-CULTURE FINDINGS AT VARIOUS INTERVALS (IN DAYS) AFTER INTRAVENOUS INJECTION												NOTES ON POSTMORTEM
		1 hour	1 day	2	4	9	12	20	30	40	60	80	100	
Human 37	1.0	4*	4	0	0	10	0	0	0	0	0	0		Killed 91 days. Tb. neg.
	0.001	0	0	0	0	0	0	0	0	0	0	0		Killed 91 days. Tb. neg.
	0.000,001	0	0	0	0	0	0	0	0	0	0	0		Killed 91 days. Tb. neg.
Bovine 39	1.0	4	5	0	0	0	0	0						Died 22 days. Miliary tb.
	0.001	0	0	0	0	0	0	0	0	0	0	0		Killed 93 days. Tb. neg.
	0.000,001	0	0	0	0	0	0	0	0	0	0	0		Killed 93 days. Tb. neg.
Avian 3	1.0	3	3	3	3	3	3							Died 18 days. Tb. 4
	0.001	4	0	0	7	7	0	0	0	5	0	0	0	Killed 105 days. Tb. 3
	0.000,001	0	0	0	0	0	0	0	0	0	0	0	0	Killed 106 days. Tb. ques.

* The numeral indicates the number of weeks of incubation after which the first positive culture was obtained in any of the tubes used.

The tuberculous involvement was graded from negative, indicating the absence of any macroscopic pathologic changes, to 4, indicating a massive generalized disease involving all the internal organs and characteristic for the disease with the particular strain under consideration and in the animal used. The avian bacillus produces a disease differing distinctly in nature from that of the human and bovine bacilli.

routes of infection, showed a persistence of the bacilli in the blood until an acute termination, usually within 20 to 40 days, without characteristic tubercle-formation, but rather with evidences of acute intoxication with diffuse splenomegaly. The intermediate dose, 0.001 mgm., of avian bacilli produced no pathological changes characteristic of tuber-

culosis in the guinea pig, while as little as 0.000,001 mgm. of virulent human or bovine bacilli produced generalized disease in the guinea pig,

TABLE 4

The presence of tubercle bacilli in the blood of chickens following the intravenous (wing-vein) injection of varying amounts of virulent human, bovine and avian tubercle bacilli

STRAIN OF BACILLI	AMOUNT INJECTED INTRAVENOUSLY IN MGM.	BLOOD-CULTURE FINDINGS AT VARIOUS INTERVALS (IN DAYS) AFTER INTRAVENOUS INJECTION												POSTMORTEM NOTES
		1 hour	1 day	2	4	9	12	20	30	40	50	60	80	100	
Human 37	1.0	4*	4	5	8	0	0	0	0	0	0	0	0		Killed 91† days. Tb.‡
	0.001	0	0	0	0	0	0	0	0						Died 38 days. Tb. neg.
	0.000,001	0	0	0	0	0	0	0	0						Died 37 days. Tb. neg.
Bovine 39	1.0	3	7	10	0	0	0	0	0	0					Died 43 days. Tb. neg.
	0.001	7	0	0	0	0	0	0	0	0	0	0	0		Killed 93 days. Tb. neg.
	0.000,001	0	0	0	0	0	0	0	0	0	0				Died 59 days. Tb. neg.
Avian 3	1.0	3	3	5	3	3	3	2	2						Died 30 days. Tb. 4 miliary
	0.001	0	0	0	0	0	0	0	7	8	3	3§			Died 57 days. Tb. 3
	0.000,001	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 112 days Tb. neg. ¶

* The numeral indicates the number of weeks of incubation after which the first positive culture occurred.

† The tuberculous findings are recorded from negative, indicating no macroscopic tuberculosis in any of the organs, to 4, indicating a massive tuberculous involvement of the important internal organs, dependent on the type of organism as to the character of the lesions found.

‡ This chicken revealed an avian tuberculosis with gross lesions in the liver and spleen of spontaneous origin.

§ 56 days.

¶ The liver and spleen of this chicken gave positive cultures for avian bacilli. This is a common finding when the organs (liver and spleen) are cultured for the first three months after intravenous injection of as little as 0.000,001 milligram of human, bovine, or avian bacilli.

without, however, a return of the bacilli to the circulation, or even their detectable presence in the blood at any time after intravenous injection.

The findings recorded in table 3 for the rabbit make it evident that

tubercle bacilli are not to be found in the circulation consistently after intravenous injection except after relatively large doses of a highly virulent strain for the animal in question when an early termination with

TABLE 5

The presence of tubercle bacilli in the circulating blood of dogs following the intravenous (ear-vein) injection of varying amounts of virulent human, bovine, and avian tubercle bacilli

STRAIN OF BACILLI	AMOUNT INJECTED INTRAVENOUSLY IN MGM.	BLOOD-CULTURE FINDINGS AT VARIOUS INTERVALS (IN DAYS) AFTER INTRAVENOUS INJECTION													POSTMORTEM NOTES
		1 hour	1 day	2	4	7	10	15	20	30	40	60	80	100	
Human 37	1.0	3*	3	4	4	4	4	7	4	3					Died 36 days.† Acute atrophy liver. No gross tubercles
	0.001	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 108 days. Tb. neg.
	0.000,001	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 108 days. Tb. neg.
Bovine 39	1.0	3	3	4	7	0	0	4	4	3					Died 30 days. Acute atrophy of liver‡
	0.001	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 108 days. Tb. neg.
	0.000,001	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 108 days. Tb. neg.
Avian 3	1.0	3	3	4	0	6	0	0	0	0	0	0	0	0	Killed 106 days. Tb. neg.
	0.001	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 106 days. Tb. neg.
	0.000,001	0	0	0	0	0	0	0	0	0	0	0	0	0	Killed 106 days. Tb. neg.

* The numeral indicates the number of weeks of incubation required for the first positive culture to develop.

† The tuberculous findings are recorded from negative, indicating no macroscopic tuberculosis was found in any of the organs, to 4, indicating a massive involvement of the important internal organs. The dog, being relatively insusceptible to even human or bovine infection, revealed an acute yellow atrophy of the liver with generalized icterus with the large doses, which might terminate in some cases without the presence of macroscopic tuberculosis being evident in the organs.

‡ Pinpoint tubercles in lung and liver.

massive acute disease is evident. Even in evident miliary tuberculosis of the rabbit, bacilli need not be found constantly in the circulation.

Table 4, listing chickens, shows that, except with large injections, the

bacilli were rarely found in the circulating blood, even though the division of the bacilli in fine, carefully prepared suspensions were of smaller size than would occur under natural conditions, and even were the bacilli to multiply in the blood free from tissue factors. It is evident also that, in the terminal stages of the disease, avian bacilli may be regularly found in the circulation, as occurred following the 0.001-mgm. dose, the blood being positive for about two weeks before death.

Although the dog did not prove to be entirely satisfactory for the purpose of studying tuberculous bacillaemia, because of the high susceptibility of its liver to acute intoxication with large amounts of tubercle bacilli, and the animal's relative insusceptibility to tuberculosis when smaller amounts of tubercle bacilli were injected intravenously, this animal bears out in general the findings obtained in the other animals. Even large doses may be removed from the circulation unless the animal succumbs to an early acute tuberculosis or an early acute organic intoxication (acute yellow atrophy of the liver), when the bacilli may remain in the blood or disappear for only a short time. However, there does not appear to be any evidence that the bacilli actually multiply in the circulating blood under any circumstances in these animals.

DISCUSSION

To infer from these experiments that tuberculosis in man and animals is a bacillaemia would appear to be drawing conclusions unjustified from the experimental facts, since only in massive overwhelming intravenous infections leading to early death of the animal do the tubercle bacilli persist in the circulation from the time of injection until the animal's death, which usually occurs within the first month after injection. There is no evidence to support the contention that the bacilli multiply in the blood even under these circumstances, but rather that the tissues are overwhelmed by the acute reaction to the highly virulent bacilli and are, therefore, unable to react to these bacilli as they would to an equal amount of avirulent bacilli by removing them from the circulation. If tuberculosis were a bacillaemia, in the exact definition of the term, there should be no reason why all the bacilli should rapidly disappear from the circulation when introduced in definitely highly infectious amounts (0.001 mgm., see tables) capable of producing a massive generalized tuberculosis, and resulting in the more progressive type of disease with a return of the bacilli to the circulation shortly before death. This is also associated with the presence of multiple ulcerative or caseating

lesions; and the return to the circulation in this case would be, therefore, rather in the nature of a tuberculous embolaemia. For the purpose of clarity, it would appear better to refer to the condition existing in tuberculosis and occurring as a transitory phenomenon, and possibly intermittently during the course of the disease or rarely present until the disease has assumed a more or less acute phase accompanied by extensive lesions or by actual generalization as an embolaemia. This would be more in line with an exact appraisal of experimental data and, especially, in view of the extensive data recently accumulated on man disproving the common occurrence of bacillaemia.

That the virulence of the bacilli for the particular animal under consideration plays a part in the persistence of the bacilli in the circulation following the injection of large doses, bearing out the observations of Hess, is evident. But to conclude that because bacilli have been found in the circulation a number of days or even weeks after the intravenous injection of large amounts of fine suspensions would define these bacilli as virulent for the species in question might be misleading and unjustified. Virulence can only be estimated from the production of progressive disease subsequent to the injection of appropriate doses of tubercle bacilli.

Regardless of the strain of tubercle bacilli or the species of animal, there appears to be a certain parallelism in all these results with graded amounts of the bacilli given intravenously, and these results are determined by the organic nature of the animal, the virulence of the strain of tubercle bacilli for the animal in question, and the amount of bacilli injected intravenously. Virulence for another species of animal plays no part in the outcome (it is individual) for the strain of the bacilli and the animal species.

On the basis of our experimental observations correlated with pathological experiences, some of which are to be published in the near future, we prefer to regard tuberculosis as a self-limited local disease with embolic and phagocytic transport tendencies showing relative immune protection against new plants, but with no retroactive effect on the first lesions, usually spreading by lymphatic and canalicular continuity with close correlation to the actual amount of bacilli present.

SUMMARY

1. Fine suspensions of virulent tubercle bacilli of the human, bovine, or avian strain injected intravenously into guinea pigs, rabbits, chick-

ens and dogs disappear from the circulation rapidly when injected in amounts of 0.001 or 0.000,001 mgm., even though these amounts are capable of producing a generalized progressive organic tuberculosis.

2. When large amounts (1 mgm. of fine suspension) of a strain of tubercle bacilli highly virulent for the animal in question are injected, they may remain in the circulation until the early acute death of the animal from an overwhelming dose, but there is no evidence to support the claim that they multiply in the circulation. Analogous amounts (1.0 mgm.) of a strain avirulent for the animal in question disappear from the circulation, but they may be found present for a week and possibly irregularly after that time, to disappear ultimately.

3. There is a certain parallelism between the reaction of the various animal species to the intravenous injection of virulent tubercle bacilli regarding the persistence of the bacilli in the blood after large doses, but there is a striking difference in organic susceptibility of these various animals to intravenous infection.

4. From these observations and numerous previous observations in man, it appears that tuberculosis is not commonly a bacillaemia in the sense that the tubercle bacilli find frequent residence or multiply in the circulation. The bacilli can be found rarely in terminal conditions in the blood, and embolic dissemination can occur occasionally and intermittently in the course of the disease, which accounts for the multiple organic metastatic foci—an occasional embolaemia.

We are grateful to Mr. Ray Stoner for assisting with the technical details entailed in this study.

REFERENCES

(1) KALLOS, P., AND KALLOS-DEFFNER, L.: Über den Nachweis der Tuberkulose-bacillämie in Kultur und Tierversuch, Kritische Übersicht, Zentralbl. ges. Tuberk.-Forsch., 1933, xxxix, 145.

(2) BREM, W. V.: Investigation of blood for tubercle bacilli, Jour. Amer. Med. Assoc., 1909, liii, 909.

(3) CORPER, H. J., AND DAMEROW, A. P.: The question of tubercle bacilli in the blood in advanced pulmonary tuberculosis. A bacteriological study, Amer. Rev. Tuberc., 1933, xxviii, 118.

(4) COHN, M. L.: An analysis of Loewenstein's method for isolating tubercle bacilli from blood, Jour. Infect. Dis., 1933, lii, 214.

(5) SAENZ, A.: Etudes sur la bacillemie tuberculeuse recherches experimentales et cliniques, Ann. Inst. Pasteur, 1934, lii, 645; Paris letter, Jour. Amer. Med. Assoc., 1934, ciii, 1960.

(6) WILSON, G. S.: (With appendices and notes by SCHWABACHER, AKELL and WOOD.) Tuberculous bacillaemia, Special Report Series, no. 182, 1933. His Majesty's Stationery Office.

(7) FISCHER, E.: Ueberlegungen und Untersuchungen zur Frage des Vorkommens von Tuberkelbazillen in strömenden Blut, Ztschr. Hyg., 1914, lxxviii, 277.
(8) HESS, A. F.: The relation of the virulence of the tubercle bacillus to its persistence in the circulation, Arch. Int. Med., 1912, x, 577.
(9) RHEINGOLD, J. C.: The effect of feeding on the rate of removal of prodigiosus bacilli from the blood of dogs, Jour. Infect. Dis., 1930, xlvii, 130.
(10) CORPER, H. J., AND VIDAL, C. B.: The inhibitory effect of normal blood on the growth of tubercle bacilli at incubator temperature, Amer. Rev. Tuberc., 1933, xxviii, 878.
(11) CORPER, H. J., AND UYEI, N.: Further observations with a new method for cultivating tubercle bacilli—a comparison with guinea pig inoculation and Petroff's method, Jour. Lab. & Clin. Med., 1929, xiv, 393.
(12) CORPER, H. J., AND COHN, M.: The nutrient quality of eggs for growing tubercle bacilli, Amer. Jour. Hyg., 1933, xviii, 1.
(13) CORPER, H. J.: Growing tubercle bacilli, Jour. Amer. Med. Assoc., 1933, ci, 982.
(14) CORPER, H. J., AND UYEI, N.: A simple glycerol water crystal violet potato cylinder medium for diagnostic cultures of tubercle bacilli, Archives Pathol., 1929, vii, 835.
(15) CORPER, H. J., AND COHN, M. L.: Maintaining water and air balance during prolonged incubation, Jour. Lab. & Clin. Med., 1934, xix, 899.

THE ORIGIN OF PULMONARY TUBERCLES IN INTRA-PULMONARY LYMPHOID TISSUE[1]

J. ZEYLAND

It was the simplicity of Huebschmann's conception of the tubercle histogenesis consisting in a successive ranging of the different tuberculous lesions (exudation—necrosis—proliferation) which induced many authors (Benda, Nicod, Seemann, Huguenin and Delarue, Bezançon and Delarue) to endorse this theory.

In some cases of miliary tuberculosis the genesis of different tubercle types is, indeed, only conceivable in the light of this theory, as may be seen, for instance, from microphotograph 1 illustrating a case of generalized miliary tuberculosis in a child deceased in its twelfth month. As shown by the microphotograph, two types of miliary foci are found in the lungs, lying sometimes close together; some are of the exudative type (caseous pneumonia) with rare acid-fast bacilli; others, less frequent, present productive-fibrous tubercles with giant cells, but without visible bacilli. The simultaneous appearance of both types can only be explained by a nonsynchronous spread of bacilli. The productive-fibrous foci originate from a more ancient spread, while the exudative foci come from a quite recent and, in the case quoted above, deadly spread.

Some workers have questioned, as known, the general value of Huebschmann's theory, pointing, among other factors, to the possiblity of a genesis of the tuberculous foci from primary productive tubercles in accordance with the opinion established previously by Baumgarten (partially Delarue, Pagel and others).

The impossibility of the application of Huebschmann's theory becomes evident in cases of experimental tuberculosis, which allow us to observe much earlier periods of tuberculous foci than those handled by the pathological anatomist who analyzes exclusively human necropsic material. Huebschmann deliberately refrained in his inferences from considering the results of experiments on animals; and this is, I am afraid, the weak side of his doctrine, because thus the very earliest periods of

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the genesis of tubercle are not taken into consideration. If we take into account this earliest period of the tubercle observed in experimental tuberculosis, we arrive at a more liberal conception of the histogenesis of tubercle, and we must accept not one, but multiple ways for its genesis.

The microphotographs 2 to 6 represent various types of the initial periods of experimentally induced pulmonary tubercles.

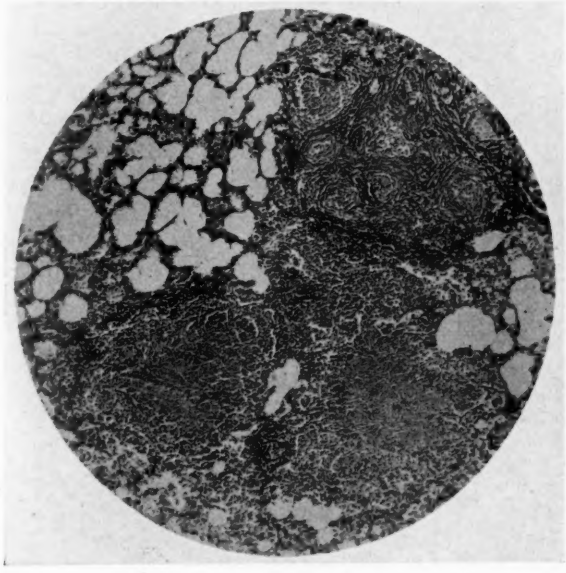

FIG. 1. Miliary tuberculous foci in 12-month-old child presenting two types: above, one productive-fibrous tubercle with giant cells; below, two foci purely exudative with caseification.

One of these varieties and, simultaneously, one of the earliest periods of a lung tubercle, undervalued in literature, is represented by the origin of the lung tubercle in the intrapulmonary lymph follicle. Coulaud, when describing the pulmonary lesion in the rabbit after the inhalation of dead tubercle bacilli and of living *BCG* bacilli, asserts having observed tuberculous lesions in intrapulmonary lymph follicles only after inhalation, but never after infecting laboratory animals by any other way.

By means of a rapid diagnosis of tuberculosis arrived at by inoculation of the suspected material directly into the inguinal lymph nodes of guinea pigs (method applied by Mrs. E. Piasecka-Zeyland) and by the early killing of these animals after finding acid-fast bacilli in the lymph nodes,

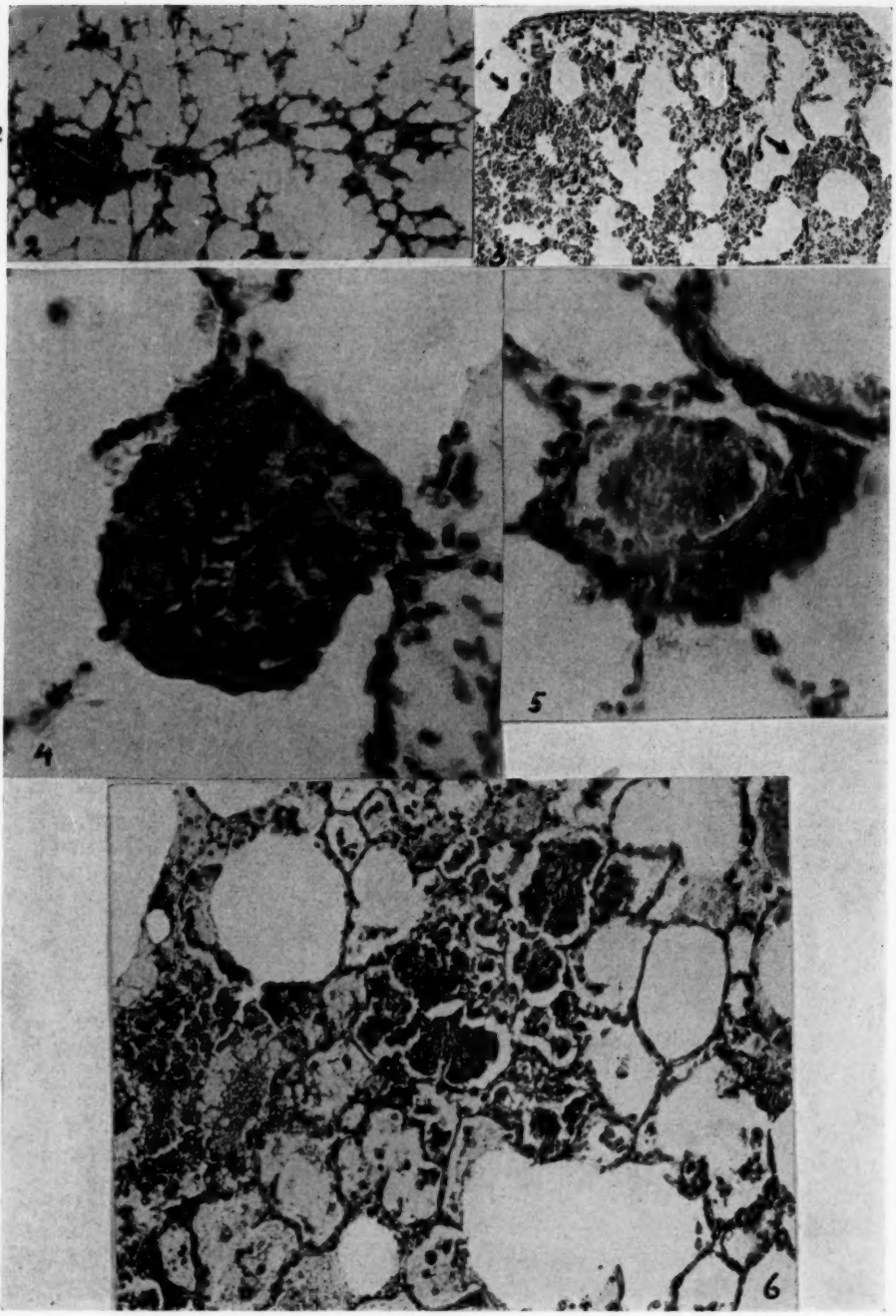

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIGS. 2–6

FIG. 2. Interstitial tuberculous lesions (filled with bacilli) in a guinea pig, one month after infection.

FIG. 3. Aggregation of granulocytes (filled with bacilli) in interalveolar septa in a guinea pig 14 days after intravenous injection of 10 mgm. of bovine (Vallée) bacilli.

FIG. 4. Epithelioid tubercle as interstitial reaction around a blood-vessel in a rabbit, 22 days after intravenous injection of 10 mgm. of *BCG* bacilli.

FIG. 5. Epithelioid reaction of the wall of a blood-vessel in the same rabbit.

FIG. 6. Intraälveolar epithelioid tubercles and so called *alveolitis desquamativa* (emigration of monocytes and exfoliation of epithelium) in a rabbit, one month after an intravenous injection of 10 mgm. *BCG*.

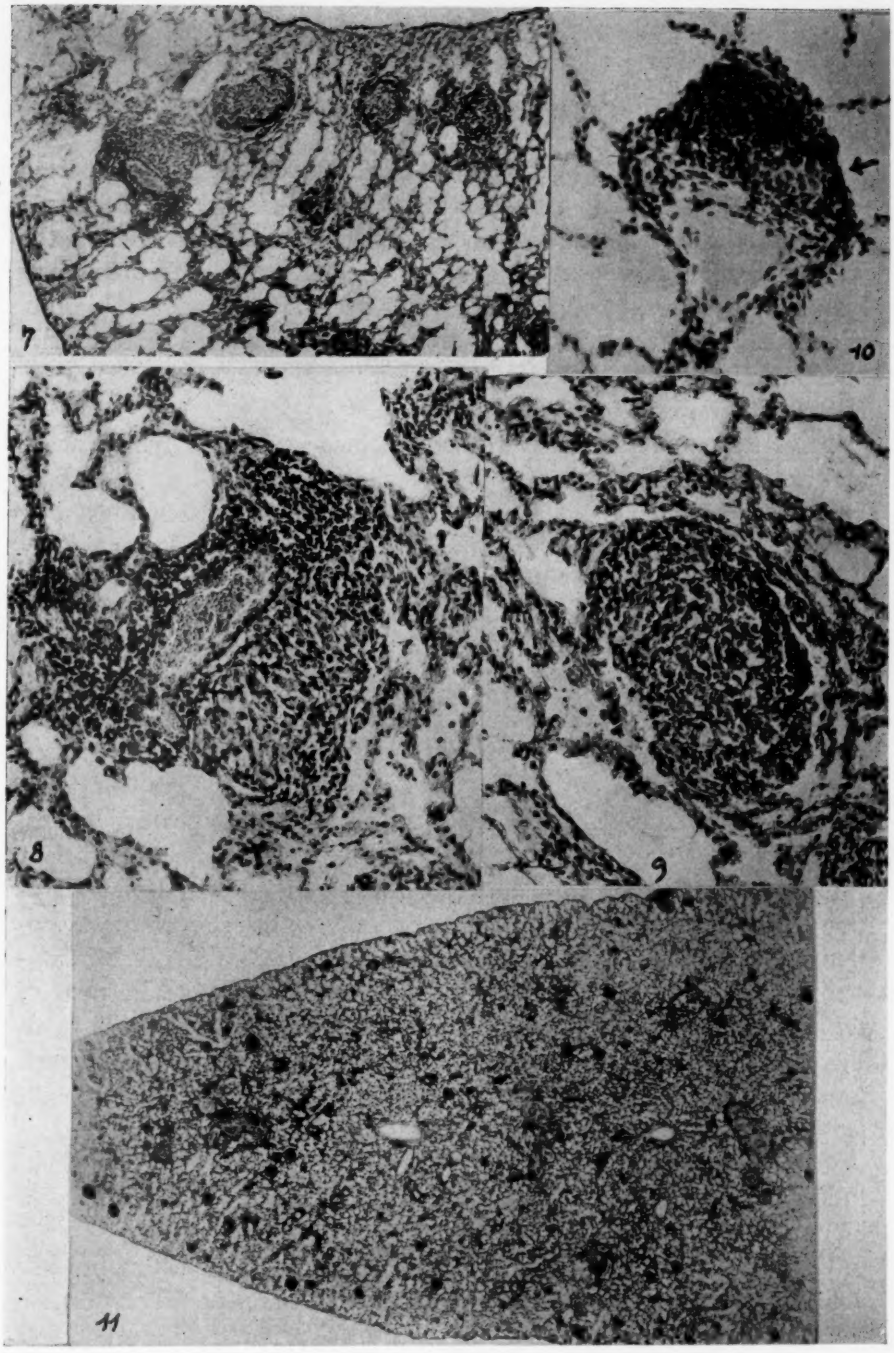

FIG. 7

FIG. 10

FIG. 8

FIG. 9

FIG. 11

FIGS. 7–11

FIG. 7. Epithelioid tubercles in intrapulmonary lymph follicles in a guinea pig, 23 days after subcutaneous infection.

FIGS. 8 & 9. Two foci of the preceding preparation at a higher power.

FIG. 10. Aggregations of epithelioid cells, with bacilli in an intrapulmonary lymph follicle around a blood-vessel in a rabbit, 15 days after intravenous injection of 10 mgm. of *BCG* bacilli.

FIG. 11. The aspect, at a low power, of the lungs of a normal 4-year-old guinea pig with many spherical intrapulmonary lymph follicles.

I have had the opportunity of examining microscopically many infected guinea pigs in very early periods of their tuberculous disease. I became convinced that in such conditions, very frequently and regardless of the way of infection, small aggregations of epithelioid cells in intrapulmonary lymph follicles are almost the only pulmonary lesions to be found (despite the statement of Vorwald). It is only in the same places that tubercle bacilli can be detected. Examples of observed lesions are illustrated by microphotographs 7 to 10.

These lesions originate like the tuberculous foci in the lymph nodes and the spleen, where, despite the observations of Joest and Emshoff, I saw frequently the first tuberculous lesions in the follicles of the lymph nodes or in the Malpighian bodies in the spleen. They consist, as already described by the above quoted authors, with reference to their inter- or parafollicular tubercles, in the earliest stage only of an aggregation of epithelioid cells; and it is impossible to discover distinctly exudative lesions either in human beings or in laboratory animals. Huebschmann, in his chapter on tuberculosis of lymph nodes and the spleen, while pointing out that his observations concern exclusively changes in diseased human beings, denies the primary existence of epithelioid cells in these organs, and describes supposed primary exudative inflammatory lesions, but never without coexisting necrosis. Necrosis seems to me a sufficient reason to consider those exudative lesions as a rather secondary immigration of the granulocytes. Such lesions, as I observed, are very exceptional in organs like the spleen and the lymph nodes. I found them myself only once: in the spleen of a young girl deceased in her 13th year of tuberculosis of adult type, there were quite small areas of necrosis with slight infiltration of granulocytes, without signs of epithelioid cell formation and without acid-fast bacilli, always outside of the Malpighian bodies.

Microphotograph 12 represents a case of an early stage of epithelioid tubercles principally on the lymph follicles (corpuscles of Malpighi) of a human spleen.

The peculiarity of the lymph follicles in the lungs, consisting in their ability to catch tubercle bacilli, was for the first time (I omit on purpose the remark of H. Albrecht on the localization of primary tuberculous foci in the smallest bronchial lymph nodes, which was only a supposition) pointed out by Krause. In connection with the rôle played by the intrapulmonary lymphoid tissue in the localization of tubercle bacilli, he developed his well-known theory on the pathogenesis of tuberculosis.

Without going into a criticism on the totality of Krause's doctrine, I

should like to pick out only one problem, namely the relation of anthracosis of the lungs to their lymph follicles, studied especially by Willis.

While examining systematically in this respect the lungs of all guinea pigs which showed no pathological modifications or only small ones, I counted the dust cells in many fields, noted their average number in one field and also estimated the number of well-developed, that is, spherical lymph follicles.

The results are as follows:

FIG. 12. Epithelioid tubercles, principally in Malpighi's corpuscles of the spleen, in an 8-month-old child, deceased of generalized miliary tuberculosis.

Of 129 guinea pigs with prominent pulmonary anthracosis, 108 (84 per cent) guinea pigs showed well-developed lymph follicles, while 21 (16 per cent) guinea pigs showed no distinct lymph follicles: of 41 guinea pigs without anthracosis, 12 (29 per cent) guinea pigs showed well-developed lymph follicles, while in 29 (71 per cent) guinea pigs no distinct lymph follicles were found.

It seems to result therefrom that the dependence of the development of pulmonary lymph follicles in guinea pigs upon the degree of anthracosis is essentially correct.

After submitting 20 guinea pigs to the action of carbon-dust and comparing their pulmonary modifications with those of 20 guinea pigs of the same age, but bred in the country under conditions as free as possible

from dust and soot, I observed, like Willis, that it is impossible to induce experimentally such striking lung anthracosis as caused spontaneously with age. Three- to four-year-old normal guinea pigs show both very distinct anthracosis and well-developed lymph follicles (microphotograph 11).

After examining systematically the lungs of autopsied children with regard to this problem I stated that there are no intrapulmonary lymph follicles in children in the first three months of life; that is, in the period, in which the foci of a tuberculous spread by the blood-stream never show a productive structure.

CONCLUSIONS

1. Only a part of tuberculous foci in the lungs undergo development through successive periods of exudative, necrotic and productive lesions, as outlined by Huebschmann.

2. A part of tuberculous foci in the lungs develop from primary epithelioid tubercles in intrapulmonary lymph follicles due to the spread of tubercle bacilli by the blood-stream.

3. According to the statements of Krause and his co-workers, the development of the intrapulmonary lymph follicles in the guinea pig depends chiefly upon the degree of anthracosis, old normal guinea pigs showing a more distinct anthracosis and larger lymph follicles in the lungs than do young animals experimentally dusted.

REFERENCES

ALBRECHT, H.: Wien. klin. Wchnschr., 1909, 327.
BENDA, C.: Annales anat. Path., 1926, iii, 945.
Med. Klinik, 1929, xxv, 971.
BEZANÇON, F., AND DELARUE, J.: Presse Méd., 1930, 369.
COULAUD, E.: Rev. Tuberc., 1933, 673.
DELARUE, J.: Les formes anatomo-cliniques des "granulies" pulmonaires, Paris, 1930.
HUEBSCHMANN, P., AND ARNOLD: Virch. Arch., 1923, ccxlix, 165.
HUEBSCHMANN, P.: Die pathologische Anatomie der Tuberkulose, Berlin, 1928.
HUGUENIN, R., AND DELARUE, J.: Annales d'Anat. Path., 1929, vi, 1181.
JOEST, E., AND EMSHOFF, E.: Virch. Arch., 1912, ccx, 188.
KRAUSE, A. K.: Amer. Rev. Tuberc., 1926, xiv, 270. (With references of all of author's and his co-workers' papers.)
NICOD, J.-L.: Annales d'Anat. Path., 1926, iii, 968.
PAGEL, W.: Die allgemeinen pathomorhologischen Grundlagen der Tuberkulose, Berlin, 1927, & Beitr. Klin. Tuberk., 1932, lxxix, 383.
PIASECKA-ZEYLAND, E.: Nowiny Lek., 1933, xlv, 545, & Beitr. Klin. Tuberk., 1935, lxxxvi, 328.
SEEMANN, G.: Ztschr. Tuberk., 1933, lxvii, 437.
VORWALD, A. J.: Amer. Rev. Tuberc., 1933, xxvii, 270.
WILLIS, H. S.: Ibid., 1922, vi, 798.

THE IMMUNIZATION OF GUINEA PIGS WITH HEAT-KILLED AND FORMOL-KILLED TUBERCLE BACILLI[1]

ARNOLD BRANCH AND JOHN F. ENDERS

These experiments on the immunization of guinea pigs with killed tubercle bacilli administered by different routes are presented, not because they offer any striking innovation in method or novelty in outcome, but because they bear directly upon two problems of special interest today to the student of tuberculosis, which, for their final solution, will depend upon the accumulation of the experimental data of the laboratory and the findings of the clinic obtained by many workers over a prolonged period. On the one hand, our experiments are pertinent to the problem of developing a safe and efficient method of prophylactic vaccination, while, on the other, they furnish a small addition to the present far too scanty body of factual material upon which the vexed question of the relationship of allergy to immunity must ultimately be decided.

It is not our purpose here to review the large bodies of literature which concern either different methods of vaccination or the evidence relating to the rôle of allergy in immunity to tuberculosis. In respect to prophylactic vaccination it is sufficient to note that the possibility of the resumption of virulence within the body by the living avirulent *BCG* vaccine of Calmette has stimulated certain workers to continue the search for an equally efficacious vaccine composed of killed tubercle bacilli. That a certain degree of immunity results from the injection of killed cultures is now recognized. For example the demonstration of a relative immunity in guinea pigs vaccinated with tubercle bacilli killed by heating to 100°C. has been given by Zinsser, Ward and Jennings (1), Petroff, Branch and Jennings (2), and very recently by Thomas (3). In his experiments Thomas also employed organisms treated with formalin. In 1933 Soper, Alpert and Adams (4) compared the immunity produced in rabbits as a result of injecting *BCG*, a virulent living

[1] From the Departments of Pathology and Bacteriology, Harvard University Medical School, Boston, Massachusetts.

human strain (H37), and "S" organisms of a bovine strain killed by heat at 100°C. These authors found that the heated vaccine was as effective as *BCG* in increasing that animal's resistance to subsequent infection with living bovine tubercle bacilli. Petroff and Steenken (5) had earlier shown that in guinea pigs heat-killed virulent human tubercle bacilli were as effective in inducing immunity as *BCG* when both vaccines were introduced parenterally. No immunity could be detected after the administration of *BCG per os*. In 1929 Rich and McCordock (6) challenged the view, more or less generally accepted since the time of Koch's fundamental observations, that the allergy of tuberculosis represented a defensive response to the invasion of the tubercle bacillus. Rich appears to regard allergy in most cases as a definitely disadvantageous factor in the disease. This conception which he has supported by experimental evidence in a series of papers[2] has recently received a certain amount of confirmation in the extensive investigations of Myers and Harrington (7) on the development of tuberculosis in children whose allergic status had been previously determined. Contrary to the conclusions of Heimbeck (8), who carried out a study similar in plan, Myers and Harrington are inclined to regard allergic tissues as exhibiting definitely less resistance to infection than those of the normal non-infected body.

Our specific objectives in the experiments about to be described were (1) to determine whether or not there was a quantitative difference in the immunity obtained after vaccination by the intravenous, the intramuscular and the intraperitoneal routes; (2) to compare the value of vaccines consisting of tubercle bacilli killed by heat at 65°C. and by the addition of formalin; (3) to ascertain whether or not there appeared to be any correlation between the time of survival of an animal and the presence of the allergic state as denoted by a cutaneous response to the injection of tuberculin resulting from vaccination and existing previous to infection.

MATERIALS AND METHODS

The organisms used throughout were from month-old egg cultures of the virulent human strain, H37. The infecting dose was 1000 organisms given subcutaneously. The heat-killed vaccine was prepared by heating a suspension of tubercle bacilli containing 6 mgm. net weight of

[2] A bibliography of the published work of Rich and his associates, as well as a summary of Rich's views on this subject, will be found in a paper in *The Lancet, 1933, ccxxv, 521.*

the organisms per cc. of salt solution at 65°C. for four hours. The formol-killed vaccine was prepared by adding 0.25 per cent formalin to a similar emulsion and allowing this to stand at room temperature for at least a week. The tuberculin was a two-months-old synthetic broth filtrate of H37 concentrated in the incubator at 37°C. to about one-fourth volume and passed through a Berkefeld-V filter. The guinea pigs were a mixed lot of males, weighing between 400 and 650 gm. In dividing them into groups, care was taken to ensure relative numbers of light and heavy animals in each group.

The intramuscular inoculations of the vaccines were made into the thigh muscles, 0.5 cc. of a 6-mgm. suspension. The same amount was given in the intravenous inoculations, which were introduced into the ear.

EXPERIMENTAL

On February 18, 1930, seventy-five guinea pigs, skin-test negative to 0.1 cc. of 1 per cent tuberculin, were divided into 5 groups as follows:

1: Controls
2: Vaccinated intravenously with heat-killed tubercle bacilli
3: Vaccinated with the same emulsion intraperitoneally
4: Vaccinated with the same vaccine intramuscularly
5: Vaccinated with formol-killed organisms intramuscularly

The vaccines were given on three occasions,—February 19 and 25 and April 22. Each dose contained 3 mgm. of tubercle bacilli in 0.5 cc. of salt solution.

Results of skin tests following vaccination: Skin tests were performed with 5 per cent tuberculin on two occasions, namely, one month after the first two vaccinations and one month following the third. The percentages of positive readings are given in table 1, in which it will be seen that the intraperitoneal route gives a larger ratio of positives

TABLE 1

Percentage of positive skin tests following vaccination by different routes

DATE	CONTROLS	HEAT-KILLED VACCINE			FORMOL-KILLED VACCINE
		Intravenous	Intraperitoneal	Intramuscular	Intramuscular
March 20.....	0	0	50	25	25
May 21.....	0	14	77	6	20

TABLE 2

Summary of results in the five groups of guinea pigs

1: CONTROLS				HEAT-KILLED VACCINE												FORMOL-KILLED VACCINE			
				2: Intravenous				3: Intraperitoneal				4: Intramuscular				5: Intramuscular			
Number	Days of life	Cause of death	Degree of tuberculosis	Number	Days of life	Cause of death	Degree of tuberculosis	Number	Days of life	Cause of death	Degree of tuberculosis	Number	Days of life	Cause of death	Degree of tuberculosis	Number	Days of life	Cause of death	Degree of tuberculosis
89	190	?	++	88	267	Tb.	+++	58	179	Tb.	++++	77	206	Tb.	+++	83	221	Tb.	+++
94	193	Tb.	++++	24	295	Tb.	+++	82	246	Tb.	+++	62	367	Subcutaneous abscess	0	14	227	Pneu.	++
86	200	Tb.	+++	18	330	Tb.	+++	95	267	Tb.	++	39	375	Pleurisy	++	234	329	Tb.	+++
70	210	Tb.	++++	11	335	Tb.	+++	219	372	Tb.	+++	26	424	Tb.	+++	21	339	Tb.	++++
60	233	Tb.	++++	72	347	Tb.	+++	53	397	Tb.	+++	61	466	Tb.	+++	3	466	Tb.	+++
13	259	Tb.	++++	9	41	Tb.	+++	68	417	Tb.	+++	46	500	?	0	66	528	Tb.	++++
33	267	Tb.	++++	54	438	?	+	218	449	Tb.	+++	85	634	Killed	0	32	569	Pneu.	+
100	298	Tb.	+++	52	466	Tb.	+++	71	535	Tb.	+++	91	634	Killed	±	69	634	Killed	+
50	301	Tb.	+++	92	537	?	++	87	634	Killed	+	81	634	Killed	0				
12	316	Tb.	+++	43	570	?	±	57	634	Killed	0								
74	349	Tb.	+++	1	634	Killed	±												
51	356	Tb.	+++																
55	634	Killed	0																
Average: 13 = 293 days				Average: 11 = 424 days				Average: 10 = 413 days				Average: 9 = 471 days				Average: 8 = 414 days			

++++ = Fulminating, generalized tuberculosis; that is, large spleens and allergic phenomena.
+++ = Generalized tuberculosis, or one organ sufficiently involved to cause death.
++ = Less.
+ = Lymph-node tuberculosis, with or without tubercles in spleen.
± = Fibrous, enlarged lymph node; probably healed tuberculosis.
0 = No gross tuberculosis.

than do the intravenous or intramuscular routes. This has previously been pointed out (9). As will be demonstrated later, the animals which exhibited no preinfected allergic skin reactions nevertheless showed indications of immunity to inoculation with virulent tubercle bacilli.

Longevity following virulent infection: On May 22, one month after the final vaccination and three months after the first, all the animals were injected subcutaneously over the belly, with 1,000 living and virulent organisms of the strain H37. In table 2 are shown the duration of life and the cause of death of the individual animals. Those that died of intercurrent infections previous to 179 days, the time at which the first animal died of generalized tuberculosis, have been excluded. All animals surviving at the end of 634 days were killed. It will be noticed from this table that a very definite increase in duration of life occurred in all the vaccinated groups of animals as compared with the controls. The average time of survival of the latter group is 293 days,

TABLE 3

Percentage of survivals at the end of one year

CONTROLS	HEAT-KILLED VACCINE			FORMOL-KILLED VACCINE
	Intravenous	Intraperitoneal	Intramuscular	Intramuscular
7.7	54.5	70	88.8	50

whereas the average time of survival of all those previously vaccinated was over 400 days. The greatest longevity occurred in the group vaccinated intramuscularly with heat-killed tubercle bacilli (471 days). This group is also interesting since five of the 9 animals at autopsy showed no gross tuberculosis. The results are somewhat vitiated by the fact that one of the controls failed to die of tuberculosis. We have not infrequently encountered this, however, when small doses were used for infection. Table 3 is appended to show the percentage survivals in each group at the end of the first year (365 days) after the infecting dose. This table brings out very well the shift to the right in the mortality curve that follows vaccination with dead organisms.

LACK OF CORRELATION BETWEEN IMMUNITY AND DERMAL ALLERGY EXISTING PRIOR TO INFECTION

An analysis of the results recorded in table 2, together with data obtained by skin tests with tuberculin prior to infection, has shown that

no significant difference exists in respect to longevity and degree of tuberculosis between the vaccinated animals which developed marked dermal sensitivity and those in which no skin response was noted. Among the 38 vaccinated animals 8 exhibited a negative or doubtful skin reaction and developed generalized tuberculosis at varying intervals after infection. In the cases of 9 others characterized by the same lack of sensitivity of the skin definite resistance to infection was apparent. Contrasting with this group, 5 animals gave severe skin reactions marked by white centres or ulceration but showed either a minimum degree of disease or remained entirely without gross evidence of tuberculosis. In the remainder strongly positive skin reactions and generalized tuberculosis were concomitantly observed.

RESULTS AND CONCLUSIONS

In accordance with the results of earlier observations, young cultures of virulent tubercle bacilli, killed by heat, have given satisfactory results as a prophylactic vaccine in guinea pigs. In the present experiments the organisms were killed at 65°C. and not at 100°C. The intramuscular route of administration of the vaccine proved more efficacious than the intravenous or intraperitoneal routes. Organisms killed by formalin were no more effective than were heat-killed bacilli. It would seem advisable to continue to assay the protective value of vaccines of dead tubercle bacilli, killed by other methods than those described, in the hope of finding a still more efficacious dead vaccine, since certain disputed points with regard to the use of avirulent living tubercle bacilli as a vaccine have hindered the universal employment of this method in either animals or man.

No correlation was found between the degree of skin-test reactivity of individual animals to tuberculin following vaccination before infection and their period of survival after infection (immunity).

REFERENCES

(1) Zinsser, H., Ward, H. K., and Jennings, F. B.: J. Immunol., 1925, xii, 97.
(2) Petroff, S. A., Branch, A., and Jennings, F. B.: Ibid., 1929, xvi, 233.
(3) Thomas, R. M.: J. Exp. Med., 1933, lviii, 227.
(4) Soper, W. B., Alpert, L. K., and Adams, M. J.: Amer. Rev. Tuberc., 1933, xxviii, 667.
(5) Petroff, S. A., and Steenken, W., Jr.: J. Immunol., 1930, xix, 79.
(6) Rich, A. R., and McCordock, H. A.: Bull. Johns Hopkins Hosp., 1929, xliv, 273.
(7) Myers, J. A., and Harrington, F. E.: Jour. Am. Med. Ass., 1934, ciii, 1530.
(8) Heimbeck: Lancet, 1927, ccxiii (2), 290.
(9) Branch, A., and Cuff, J. R.: J. Inf. Dis., 1930, xlvii, 151.

THE EFFECTS OF ADDING VARIOUS SUBSTANCES TO SUSPENSIONS OF TUBERCLE BACILLI IN EXPERIMENTAL INFECTION

C. B. VIDAL[1]

The complexity of tuberculosis is evident at every attempt to solve the intricacies of this disease, both experimentally and clinically, and especially to control the evidence at hand. Now and again, in experimental studies, the control becomes more complicated and requires more expenditure of effort than the final test itself. Again facts stand as obvious but empiric, and await later explanation for detailed understanding. The latter is well illustrated, by the effect of both local and general conditions upon the progress of tuberculosis in the human and animal economy. It is not the purpose of this report to dwell upon these well-known facts, but rather to briefly record an experimental observation in support of the significance of the local environment upon the spread of tuberculosis. The observations were part of a study suggested by the broad range of growth of tubercle bacilli on culture media, covering the extensive field from almost non-nutrient media (consisting of the simplest of chemical salts, including only ammonium citrate, simple inorganic buffers, and the non-nutrient agar when heavy plantings are used) to complicated food-stuffs, such as eggs, potatoes, and animal tissues including blood, when few bacilli are planted. Evidently the tubercle bacillus is able to survive under suitable conditions (Corper and Cohn (1) found them alive after 12 years at incubator temperature in simple glycerol-broth) for prolonged periods, and they are able to grow on an extremely simple diet *in vitro*. *In vivo*, however, conditions become more complicated, and although the factor of nutrition is well provided for by seeming highly adequate elements even for supporting the growth of small numbers of bacilli, the little-understood factors of virulence, cellular versus non-cellular residence, and other factors, such as gaseous exchange (2), complicate the problem and are not easy to control except by comparative tests alone.

For the purpose of *in vivo* comparative tests, guinea pigs were given

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subcutaneous injections of fine-graded suspensions of tubercle bacilli mixed with 2 cc. of sterile 0.9 per cent sodium-chloride solution as control. To a definite amount of this suspension was then added chemically pure and washed filter paper as a non-nutrient material, to act as a control against the various nutrients to be tried. Likewise, 2 cc. of a 2 per cent solution of agar-agar, without the addition of salt or nutrients, was used as another non-nutrient control. Two substances were used as nutrients, namely, coagulated egg-white, representing a nutrient of low value for human tubercle bacilli (3), and citrated whole rabbit's blood (4), representing a high-quality nutrient for tubercle bacilli. In

TABLE 1

*A comparison of the amount of tuberculosis found in guinea pigs after the subcutaneous injection of virulent human tubercle bacilli in saline solution mixed with filter paper, agar, coagulated egg white, or rabbit's blood**

BACILLI USED FOR INFECTING	MATERIAL MIXED WITH BACILLI	TUBERCULOUS FINDINGS IN THE GUINEA PIGS 8 WEEKS AFTER INJECTION	
		0.001 mgm.	0.000,000,1 mgm.
Human 34 from sputum	0.9% NaCl	3†	1
	Filter paper	4	2
	Agar	4	2
	Egg-white (heat-coagulated)	3	3
	Blood (rabbit citrated)	4	2

* Since the findings with the different strains, although varying in amount of tuberculosis found for the different strains, were in relative agreement, the findings for strains S4 and "Gluckson" are omitted from the tabulation.

† The tuberculous involvement found in the guinea pigs eight weeks after injection is graded from 1, indicating the involvement of the local inguinal lymph nodes alone, to 4, indicating generalized involvement of all the organs, including spleen, lungs and liver.

order to note the effect on different amounts of bacilli injected and on different strains of tubercle bacilli (laboratory and recently isolated), the guinea pigs were infected, using four to six for each test, with 0.001, 0.000,01, and 0.000,000,1 mgm. of fine suspensions of bacilli and from two strains recently isolated from human sputum (S4 and S34), and one laboratory strain (Gluckson) isolated fifteen years ago and maintained since that time on artificial media. The findings expressed in the amount of tuberculous involvement found in the guinea pigs after eight weeks are recorded in table 1.

It then appears that, although the addition of a nutrient (egg-white or rabbit's blood) to a suspension of virulent human tubercle bacilli

before injection exerts little influence upon the subsequent tuberculous involvement found in these animals eight weeks after injection as compared with similar non-nutrient materials (filter paper and agar), there is found, however, a definite and constant enhancing effect upon the tuberculosis found after the introduction of either a nutrient or a non-nutrient material, such as filter paper, agar, coagulated egg-white, or rabbit's blood, as compared with controls in which salt solution alone was used as the diluent for the bacilli. These experiments stress also the importance of controlling, in as nearly a similar manner as possible, any tests conducted in tuberculosis concerning mechanical, chemical, or nutrient effects *in vivo*.

REFERENCES

(1) Corper, H. J., and Cohn, M. L.: The viability and virulence of old cultures of tubercle bacilli, Amer. Rev. Tuberc., 1933, xxviii, 856.

(2) Corper, H. J., Lurie, M. B., and Uyei, N.: The variability of localization of tuberculosis in the organs of different animals, Ibid., 1926, xiv, 662 & 668; 1927, xv, 65, 237 & 389.

(3) Corper, H. J., and Cohn, M. L.: The nutrient quality of eggs for growing tubercle bacilli, Amer. Jour. Hyg., 1933, xviii, 1.

(4) Corper, H. J.: Growing tubercle bacilli, Jour. Amer. Med. Assoc., 1933, ci, 982.

A REPORT OF 1170 CUTANEOUS TESTS WITH FOUR TUBERCULINS[1]

CARL R. HOWSON[2]

In the twenty-seven years which have elapsed since Pirquet brought forth his cutaneous test, numerous other tests for the determination of cutaneous allergy to the products of tubercle bacilli have been devised. The conjunctival test of Calmette and Wolff-Eisner had its day. The Moro test has recently been revived in somewhat modified form. The intracutaneous test of Mantoux is rapidly becoming accepted as standard. For some unknown reason the modification of the Pirquet proposed by Detré in 1908 (1) has received scant attention in this country. To O. T. he added B. F. H. and B. F. B., having in mind the possibility that in the process of concentration by heat in the manufacture of O. T. some reaction-producing thermolabile substances might be destroyed; and, further, that the addition of bovine filtrate might be of advantage in detecting cases of bovine infection. A further modification was made in 1909 by Dr. Chas. C. Browning, my former associate, to whom I am indebted for some of the figures used in this study. He added O. T. B., so that the tests used until recently in our private practice consisted of four tuberculins, namely O. T. H., O. T. B., B. F. H., and B. F. B. (2).

During the course of our work we reached certain conclusions regarding this test and the reactions obtained, and the figures here reported are the result of a study made in an endeavor to verify or disprove these.

There was no doubt in our minds as to the increased sensitiveness of the test, for we frequently observed cases in which there was no reaction to O. T. H., but definite reaction to one or more of the other tuberculins. We felt, also, that the ability of the patient to react was affected to some extent by the condition of his blood, with particular reference to the haemoglobin and red cell count (3).

The records of some 1,800 patients seen in private practice have been studied. Because of incomplete data, only 1,170 cases have been used, of

[1] Presented at the twenty-ninth annual meeting of the American Sanatorium Association, Cincinnati, Ohio, May 14, 1934.

[2] Los Angeles, California.

which only a small proportion, 167 cases, had sputum in which tubercle bacilli were demonstrated. As so many variables enter into the blood picture, only haemoglobin percentages have been used in this study.

It is of interest to note that, of patients consulting a chest specialist in Southern California because of suspected pulmonary disease, tubercle bacilli were found in the sputum in less than 15 per cent of the cases. A group of similar patients examined fifteen years ago showed an incidence of 22 per cent with positive sputum. Our present rate is under 12 per cent. Apparently both physicians and public, in Southern California at least, are becoming more "tuberculosis conscious."

The haemoglobin determinations were all made in our own laboratory and the great majority by one technician; so we feel that the margin of error due to the personal element and differences in technique is minimal.

The tuberculin used was produced by one commercial laboratory. Some years ago a small series of patients was tested simultaneously with this tuberculin, with tuberculin obtained from the laboratories of the Health Department of New York City, and with tuberculin prepared by Dr. Esmond R. Long from cultures grown on his synthetic medium. The reactions obtained were quite consistent, the synthetic medium product being apparently slightly less active than the other two preparations.

We had long noticed that reactions to O. T. B. occurred with considerable frequency, occasionally even in the absence of a reaction to O. T. H. and both bouillon filtrates; and, as the figures in this series were analyzed, we were not surprised to see that this showed up in the totals. It was, however, somewhat of a surprise to find, in 1,003 patients without positive sputum (table 1), 55.2 per cent of positive reactions to O. T. B. as compared with 39.2 per cent to O. T. H. Both B. F.'s gave fewer reactions than the corresponding O. T.'s, but B. F. B. showed about the same number (39.4 per cent) as O. T. H. (39.2 per cent). When we consider the patients with positive sputum (table 2) the difference is even more striking, the percentages being as follows:

O. T. H.	37.7%	B. F. H.	35.3%
O. T. B.	62.3%	B. F. B.	39.5%

Taking the group of 1,170 patients as a whole (table 3), the percentages of reactions are as follows:

O. T. H.	39.0%	B. F. H.	35.0%
O. T. B.	56.2%	B. F. B.	39.4%

The greater reacting power of the Old Tuberculins is probably due to the greater concentration of the tubercle proteins contained therein,

TABLE 1

Individual reactions to different tuberculins in 1,003 patients with sputum negative or absent

4,012 scarifications

HAEMOGLOBIN	O. T.	B. F.	O. T. B.	B. F. B.	TOTAL
per cent					
90–100	146	135	213	142	636
80–90	169	149	235	173	726
70–80	62	52	84	66	264
60–70	16	13	22	14	65
Total reactions.....	393	349	554	395	1,691
Per cent positive.....	39.2	34.8	55.2	39.4	42.6

TABLE 2

Individual reactions to different tuberculins in 167 patients with positive sputum

668 scarifications

HAEMOGLOBIN	O. T.	B. F.	O. T. B.	B. F. B.	TOTAL
per cent					
90–100	15	14	20	12	61
80–90	24	24	41	28	117
70–80	13	11	27	15	66
60–70	11	11	16	11	49
Total reactions.....	63	60	104	66	293
Per cent positive.....	37.7	35.3	62.3	39.5	43.9

TABLE 3

Individual reactions to different tuberculins

Total, 1,170 patients: 4,680 scarifications

HAEMOGLOBIN	O. T.	B. F.	O. T. B.	B. F. B.	GRAND TOTAL
per cent					
90–100	161	149	233	154	697
80–90	193	173	276	201	843
70–80	75	63	111	81	330
60–70	27	24	38	25	114
Total reactions.....	456	409	658	461	1,984
Per cent positive.....	39	35	56.2	39.4	42.4

as Seibert (4) has recently shown that the antigenic properties vary with the concentration of the protein. It is possible that there has been

some loss of reactivity due to heating in the process of concentration; but, if so, this is not sufficient to overcome the differences due to a tenfold concentration.

Taking the total number of patients in the series as 100 per cent, the number of reactions to O. T. B. in patients not having positive sputum was 16 per cent greater than to O. T. H., and in patients with positive sputum 24.6 per cent greater, the combined groups averaging 17.2 per cent greater (39 vs. 56.2 per cent). If we consider the total number of patients reacting to O. T. H. as 100 per cent, then the number of reacting to O. T. B. would be 144 per cent. This seems to us a rather striking phenomenon. While the reactions to B. F. B. are definitely more numerous than those to B. F. H., the difference is not nearly so great.

This difference is quite in accord with Seibert and Morley's observations (5) that they obtained larger reactions with bovine protein than with the human. They comment that this "is unexplainable at the present time, and may prove of considerable significance in future investigations." Obviously it occurs much too frequently to be of any particular significance with regard to the presence or absence of bovine infection. It has seemed to us that it occurs more frequently in cases of low grade activity and marked chronicity.

The number of individual reactions to the different tuberculins, correlated with the haemoglobin percentages, is shown in tables 4, 5 and 6. It will be noted that, of the patients having negative sputum or no sputum (table 4), positive reactions were obtained in 42.1 per cent of all the tests. Classified according to haemoglobin percentages, the reactions in the different groups were as follows:

Hb. 90–100%..... 43.2% positive reactions
Hb. 80–90%..... 44.0% positive reactions
Hb. 70–80%..... 38.2% positive reactions
Hb. 60–70%..... 31.8% positive reactions

In the group with positive sputum (table 5) the percentage of positive reactions runs slightly higher, namely:

Hb. 90–100%..... 47.7% positive reactions
Hb. 80–90%..... 47.2% positive reactions
Hb. 70–80%..... 41.2% positive reactions
Hb. 60–70%..... 37.1% positive reactions

with an average for the entire group of 43.9 per cent. A summary of the reactions obtained with the entire group of 1,170 patients, comprising 4,680 tests, (table 6) shows

TABLE 4

Individual reactions to different tuberculins

Sputum negative or absent

HAEMOGLOBIN	90–100%	80–90%	70–80%	60–70%	GRAND TOTAL
Total patients	368	412	172	51	1,003
O. T	146	169	62	16	393
B. F	135	149	52	13	349
O. T. B	213	235	84	22	554
B. F. B	142	173	66	14	395
Total reactions	636	726	264	65	1,691
Total tests	1,472	1,648	688	204	4,012
Per cent positive	43.2	44	38.2	31.8	42.1

TABLE 5

Individual reactions to different tuberculins

Sputum positive

HAEMOGLOBIN	90–100%	80–90%	70–80%	60–70%	TOTAL
Total patients	32	62	40	33	167
O. T	15	24	13	11	63
B. F	14	24	11	11	60
O. T. B	20	41	27	16	104
B. F. B	12	28	15	11	66
Total reactions	61	117	66	49	293
Total tests	128	248	160	132	668
Per cent positive	47.7	47.2	41.2	37.1	43.9

TABLE 6

Individual reactions to different tuberculins

Total

HAEMOGLOBIN	90–100%	80–90%	70–80%	60–70%	GRAND TOTAL
Total patients	400	474	212	84	1,170
O. T	161	193	75	27	456
B. F	149	173	63	24	409
O. T. B	233	276	111	38	658
B. F. B	154	201	81	25	461
Total reactions	697	843	330	114	1,984
Total tests	1,600	1,896	848	336	4,680
Per cent positive	43.6	44.5	38.9	33.9	42.4

Hb. 90–100% ..... 43.6% positive reactions
Hb. 80–90% ..... 44.5% positive reactions
Hb. 70–80% ..... 38.9% positive reactions
Hb. 60–70% ..... 33.9% positive reactions

the average for the entire series being 42.4 per cent.

The difference in the number of reactions between the two highest

TABLE 7

Patients reacting to one or more tuberculins

Sputum negative or absent

HAEMOGLOBIN	90–100%	80–90%	70–80%	60–70%	TOTAL
Total patients	368	412	172	51	1,003
Negative to all	136	160	78	28	402
Patients reacting	232	252	94	23	601
Per cent patients reacting	63	61.2	54.6	45.1	60

TABLE 8

Patients reacting to one or more tuberculins

Sputum positive

HAEMOGLOBIN	90–100%	80–90%	70–80%	60–70%	TOTAL
Total patients	32	62	40	33	167
Negative to all	8	16	12	17	53
Patients reacting	24	46	28	16	114
Per cent patients reacting	75	74.2	70	48.5	68.2

TABLE 9

Patients reacting to one or more tuberculins

Total

HAEMOGLOBIN	90–100%	80–90%	70–80%	60–70%	GRAND TOTAL
Total patients	400	474	212	84	1,170
Negative to all	144	176	90	45	455
Patients reacting	256	298	122	39	715
Per cent patients reacting	64	62.9	57.5	46.4	61.1

groups is not sufficient to be of importance, but there is a definite drop when we come to the group having haemoglobin readings of 70–80 per cent and a further definite drop in the 60–70 per cent group.

In tables 7, 8 and 9 are shown the results according to the number of patients reacting. Any patient who showed a positive reaction to one or more of the tuberculins is included in these as reacting positively. The percentages of reactions in the four haemoglobin groups in the patients above mentioned, having no sputum or whose sputum was negative (table 7), are

Hb. 90–100%..... 63.0% positive reactions
Hb. 80–90%..... 61.2% positive reactions
Hb. 70–80%..... 54.6% positive reactions
Hb. 60–70%..... 45.1% positive reactions

with an average of 60 per cent reacting. In patients with positive sputum (table 8) the percentages were definitely higher, with an average of 68.2 per cent. These four groups show, respectively:

Hb. 90–100%..... 75.0% positive reactions
Hb. 80–90%..... 74.2% positive reactions
Hb. 70–80%..... 70.0% positive reactions
Hb. 60–70%..... 48.5% positive reactions

Considering the group of 1,170 patients as a whole (table 9), of those with

Hb. 90–100%..... 64.0% reacted
Hb. 80–90%..... 62.9% reacted
Hb. 70–80%..... 57.5% reacted
Hb. 60–70%..... 46.4% reacted

Of the entire 1,170 patients, a total of 61.1 per cent reacted to one or more tuberculins.

It is to be expected that in the lower haemoglobin groups there would be present a greater percentage of complicating conditions or far-advanced cases, which would tend to affect the patient's ability to react. However, the number of far-advanced cases in this series is so small, and the findings so consistent, that we feel this does not vitiate the conclusions.

It is realized that the number of patients in this series is too small to draw conclusions which are other than suggestive.

SUMMARY

1. The results of cutaneous tests with four tuberculins applied to 1,170 patients seen in private practice are reported.

2. Only 39 per cent of the patients reacted to O. T. H., while 56.2

per cent reacted to O. T. B., the latter giving 44 per cent more positive reactions than the former. The reason for this difference is not apparent, but would seem to justify further studies.

3. In this group of patients, 39 per cent reacted to O. T. H. By the use of three additional tuberculins the number of reactors was raised to 61.1 per cent, an increase of 56 per cent.

4. A low haemoglobin seems to definitely impair the individual's ability to react to the cutaneous application of tuberculin.

REFERENCES

(1) Detré, L.: Differenticle Tuberkulin-Reaktionen, Wien. Klin. Wchnschr., 1908, xxi, 173.
(2) Ryan, L. M.: Tuberculin as a diagnostic test of tuberculosis in man, Jour. Am. Med. Assoc., 1918, lxx, 982.
(3) Browning, C. C.: Value of the tuberculin cutaneous test, Northwest Med., 1919, xviii, 230.
(4) Seibert, Florence B.: Chemical composition of the active principle of tuberculin, Jour. Inf. Dis., 1932, li, 383.
(5) Seibert, Florence B., and Morley, Nelle: The relationship of the tuberculin proteins of different acid-fast bacilli to sensitization as indicated by their reactivity in sensitized animals, Jour. Immunol., 1933, xxiv, 149.

WHOOPING-COUGH IN TUBERCULOUS CHILDREN[1]

J. IVAN HERSHEY AND FRIEDA WARD

Whooping-cough has long been considered one of the more serious diseases of childhood because of the untoward complications and sequelae which so frequently arise, and among these pulmonary tuberculosis is not uncommon. The accepted teaching has been that whooping-cough serves to arouse to activity a latent tuberculous process already present. Jones (1), in his review of the literature on the subject, states that 5 per cent of all cases of whooping-cough develop tuberculosis as a sequel. Furthermore, it is rather generally believed that the occurrence of pertussis among clinically active cases of tracheobronchial tuberculosis alters the outlook considerably and causes the prognosis to be very grave.

This past year, during the occurrence of a small epidemic of whooping-cough among the children at the Eagleville Sanatorium, an opportunity was afforded us to make some interesting observations relative to the course and effect of this disease in tuberculous children. The classification of these children can be considered under three general headings; namely (1) those with tracheobronchial tuberculosis (manifest disease), (2) observation cases with positive intracutaneous tuberculin reactions, and (3) known contact cases with negative Mantoux reactions and for the most part suffering from malnutrition.

A six-year-old girl, suffering from childhood-type tuberculosis was admitted from a Philadelphia hospital in March, 1934. The most prominent symptom was a moderately severe cough, the nature of which did not seem unusual at the time. However, this symptom became more pronounced and was accompanied by vomiting, and when two other children of the same ward developed a similar cough, cough-plate cultures on Bordet-Gengou medium (one part human blood to three parts of potato-agar base) were made and were found to show the typical haemolytic colonies of *Bacillus pertussis* in all three instances. Realizing the possible serious consequences of a threatening epidemic, immediate isolation was effected and cough-plate cultures made on all contact cases, one of which showed the organism at this time. At the time quarantine was

[1] From the Eagleville Sanatorium, Eagleville, Pennsylvania, A. J. Cohen, Medical Director.

established there were 31 children, aged four to fifteen years, in this unit, thirteen of whom gave a definite past history of pertussis. Within the first few days, three additional children developed the disease, making then a total of 7 cases. A vaccine of this specific strain was prepared in our own laboratory with a view toward the immunization of the remaining children whose past history did not include whooping-cough, as well as to be used in the active treatment of patients developing the disease. We also included in the group for immunization all nurses and other employees who had any contact with these children and who did not have a definite history of pertussis.

This vaccine was prepared by growing the organisms on unadjusted Bordet-Gengou medium for three days. The organisms and water of condensation were then rapidly washed off with a solution of physiological saline solution containing 0.5 per cent phenol, and the suspension was standardized so that it would contain five-billion bacilli per cubic centimetre. The vaccine was now incubated at 37° C. for twenty-four hours, then cultured, and when found to be sterile it was ready for use.

Eleven children and 14 nurses and employees received the prophylactic treatment. The vaccine was given in three doses; one-billion, two-billions, and three-billions, respectively, at weekly intervals. Varying degrees of local reaction were encountered and the only general reaction seemed to be headache and drowsiness. It might be interesting to note that, of the children of this group, two later developed the infection with a mild course, one being diagnosed the day following the first prophylactic treatment. In the other instance, despite a persistent suspicious cough, confirmatory diagnosis could not be made until one week after the last prophylactic dose.

A positive diagnosis of pertussis was established in 10 cases, 9 children and one adult, who was the supervising nurse in charge of the pavilion. Of these 9 children, seven were known cases of tracheobronchial tuberculosis, one was an observation case with positive Mantoux reaction, and the other a contact case with negative Mantoux. The specific vaccine was given to these cases on alternate days, beginning with 250 million organisms and gradually increasing the dosage to three billions. Reactions to the vaccine therapy were limited to slight and moderate local reactions. In addition, the usual sedative and symptomatic treatment was employed. Under this therapy the symptoms were definitely ameliorated in all of the cases, and in two children and the one adult the disease was practically aborted.

The course of each patient was followed by daily haemograms, and in the more clinically active types marked leucocytosis was found with a high percentage of lymphocytes in the differential count. This was in contrast to the abortive form which showed only a slight increase in the total number of white cells with a moderate lymphocytosis, a finding not

infrequently encountered in uncomplicated tracheobronchial tuberculosis. The total leucocyte counts on our patients were not as high as frequently seen reported in the literature (2) (3), and it is felt that this may be due to the fact that vaccine therapy was instituted early in the

TABLE 1

Haemograms

	CLINICALLY ACTIVE				ABORTIVE TYPE			
Days after diagnosis	Total leucocytes	Total neutrophiles	Lympho-cytes	Monocytes	Total leucocytes	Total neutro-philes	Lympho-cytes	Mono-cytes
		per cent	*per cent*	*per cent*		*per cent*	*per cent*	*per cent*
1	14,300	51	45	4	11,750	56	40	2
2	12,700	41	54	4	9,250	56	37	6
3	21,550	57	32	8	10,850	64	29	5
4	15,950	38	57	3	11,150	68	24	6
5	21,800	38	52	9	12,350	49	40	7
6	29,800	29	66	4	9,500	59	31	10
7	30,350	36	60	3	10,100	57	35	8
8	38,400	22	74	3	13,950	50	38	9
9	35,700	19	75	5	13,600	59	31	9
10	33,300	16	79	3				
11	31,600	19	73	7	17,600	65	29	5
12	39,600	13	81	6				
13	35,600	24	65	9	11,000	66	29	2
14	44,250	32	60	6				
15	33,650	33	61	5				
16	37,600	32	63	5				
17	32,400	25	71	4	10,450	67	28	4
18	26,400	26	67	6				
20	46,200	26	65	8	13,900	59	32	8
21					11,500	61	29	9
22	26,800	27	66	6	10,450	60	33	4
24	19,100	43	51	4	9,700	64	40	4
25	15,300	39	51	10	11,000	67	28	3
27	17,500	40	55	5	11,000	69	27	4
28	15,400	34	54	12				
30	12,100	39	51	9				
32	12,750	24	68	6				
35	13,600	35	53	10				

course of the disease. Table 1 serves to illustrate the blood-picture of one of the clinically active cases compared with one of the abortive type.

As was mentioned above the total number of cases developing the disease was limited to 9 children and one adult, and quarantine was lifted

at the end of a little over ten weeks. It is interesting to note here that, of our cases, two gave a previous history of pertussis, the present attack following a rather severe clinical course in the one instance, while in the other the disease was of the mild, abortive type. Two of the 11 children receiving prophylactic treatment also developed a very mild form of the disease; as previously stated, one was diagnosed the day following the first prophylactic treatment.

Clinically, none of the children exhibited any ill-effects from the whooping-cough; in fact, most of them benefited greatly from the enforced bed-rest. Roentgenographically, six of the 9 children showed only a slight generalized accentuation of the trunk-markings of the lungs, while in the other three instances there were no changes whatsoever. The adult patient, who was an "Apparently Cured" case of tuberculosis, showed no changes clinically nor roentgenographically. These results were noted after a period ranging from three to ten months of observation.

Without attempting to draw final conclusions, the interesting part of this experience lies in the fact that here we have whooping-cough occurring in children with known childhood type of tuberculosis and in no single instance could any serious consequence be detected by physical examination or roentgenograms. This is in marked contrast to the generally accepted view that whooping-cough is a very grave complication of latent or active pulmonary tuberculosis.

SUMMARY

A small series of cases of whooping-cough occurred among tuberculous children in a sanatorium. In each case confirmatory diagnosis was established by cough-plate cultures. A vaccine, prepared from the strain of *B. pertussis* isolated from these patients, was employed both in the prophylactic and active treatment of the outbreak. Daily haemograms were made and comparative findings noted. Contrary to the accepted view, the children showed no ill-effects from the whooping-cough, clinically nor roentgenographically.

REFERENCES

(1) Jones, J. L.: The present status of whooping-cough, Kentucky Med. J., 1928, xxvi, 644.
(2) Leitner, P.: Zur Frühdiagnose des Keuchhustens, Beitr. Haemotologie des Keuchhustins, Jahrb. Kinderhk., 1929, cxxi, 164.
(3) Abt, A. F.: Extreme leucocytosis in pertussis, Med. Clin. North America, 1931, xiv, 1229.

PRESENT CONCEPTS OF TUBERCULOUS INFECTION AND DISEASE[1,2]

Their Principles and Application

EUGENE L. OPIE

Tuberculosis is a widespread infection that in relatively few instances rises to the threshold of manifest disease. This conception is in large part based on anatomical observations made since the discovery of the tubercle bacillus. Küss found that tuberculous lesions of the lymph nodes are almost invariably associated with similar nodules in the lung substance, presumably at the site of entrance of the tubercle bacillus, and a few years later Ghon very clearly established this relationship. Accurate knowledge of the widespread distribution of tuberculous infection in persons who do not suffer with the disease dates from the observations of Naegeli made in Zurich at the beginning of the century, when he showed that anatomical evidence of tuberculous infection could be found in 97 per cent of persons over eighteen years of age. The application of the tuberculin test, by Pirquet and others, to the recognition of the tuberculous infection of children confirmed and extended knowledge of its widespread occurrence in the larger cities of Europe and North America. In his address as President of this Association in 1911, Dr. William H. Welch discussed the great frequency of tuberculous infection in early life and its significance for prevention of the disease.

TUBERCULOUS INFECTION OF CHILDREN AND OF ADULTS

Within the same period, information, gradually accumulated by pathologists, has shown that the tuberculosis of infants and young children differs conspicuously from that of adolescents and adults. The use of roentgenographic plates in the examination of lungs removed at autopsy has facilitated the discovery of calcified scars and has shown that those

[1] An address, opening a Joint Symposium on the topic, *Present Concepts of Tuberculous Infection and Disease: Their Principles and Application*, at the 31st annual meeting of the National Tuberculosis Association, Saranac Lake, New York, June 27, 1935.

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who die with the characteristic pulmonary tuberculosis of adults have demonstrable foci of healed infection in lungs and tracheobronchial lymph nodes or occasionally in mesenteric lymph nodes. There is anatomical evidence that the lesion of adult life is not the continuation of a first infection, since scars of the latter are calcified and healed, and are not in continuity with the progressive lesion that is often in the opposite lung.

The present conception of a first infection or childhood type of tuberculosis and of an adult or reinfection type has not been established so much by knowledge of immunity and sensitization or "allergy" as by anatomical observations that are readily repeated. The graph that represents deaths from tuberculosis plotted by age is especially instructive in this relation. There is a high peak in the second half of the first year of life, representing infant mortality, and this is followed by a rapid fall to a low level maintained throughout childhood, when the disease usually, though not always, pursues a benign course. With adolescence beginning, as is well known, earlier in girls than in boys, morbidity and mortality from tuberculosis increase rapidly and reach a high level that is maintained until old age approaches. The clinical course and antomical characters of the disease that produce the peak of infantile mortality in the first year of life are so different from those of the adult type that the identity of the two might be doubted if their causal agent were not universally recognized. First infection with tuberculosis is essentially the same at whatever age it occurs and the first infection of the white infant is reproduced by the first infection with tuberculosis that is often seen in adults of the negro race.

First infection with tuberculosis should not be regarded as an isolated lesion at the site of invasion of the tubercle bacillus but as a progressive disease that pursues a characteristic course. At the risk of repeating what is familiar to many, its characteristics may be cited. There is (1) tuberculous pneumonia and tubercle-formation of greater or less extent in some part of the lung, not more frequently in the apex than elsewhere (an exception to this statement will be cited); (2) implication of the adjacent lymph nodes, often with progressive enlargement and massive caseation of these structures; (3) dissemination of tubercle bacilli by way of the blood-stream, with tuberculosis of distant organs, as of spleen, liver, meninges, and (4) in many instances death with generalized miliary tuberculosis. Infection may enter the body by way of the gastrointestinal tract, usually in infants or young children, and in these instances pursues a course analogous to that outlined above.

Tuberculosis of adult type is almost invariably a disease of different character, that begins in the lungs and here produces the changes by which it is recognized: (1) It begins in the upper part of the upper lobes doubtless because the peculiar position and conformation of the adult chest and the associated physiology of respiration make these the most susceptible parts of the lungs. (2) Its tendency to remain localized in the lung, and often in the apices of the lungs, is its outstanding feature. (3) The adjacent lymph nodes show scant involvement and the gross caseation of these structures, characteristic of tuberculosis of first infection, is wanting. (4) Dissemination by way of the blood-stream is absent or inconspicuous, and miliary tuberculosis following penetration of a caseous lesion into contact with the circulating blood is an unusual and late event. (5) The disease progresses, in large part at least, by way of the bronchi from one part of the organ to another, and ultimately by way of these structures may reach the trachea, larynx and intestine. (6) The disease often pursues a chronic course and is associated with cavity-formation and fibrosis. We may justly assume that the localization of the disease in the lung is referable to the immunity conferred by a first infection, and its tendency to pursue a chronic course with fibrosis may be similarly explained.

SENSITIZATION AND RESISTANCE

We have no exact knowledge concerning the relation of anatomical changes to sensitization or "allergy," and the literature of this subject contains much, often contradictory, speculation. Animals that have received living or dead tubercle bacilli become "sensitized" to the tubercle bacillus and its products, so that an increased local injury and intensified inflammatory reaction occurs about the microörganism when it finds its way into the tissues. Parallel with these changes of sensitization, though not necessarily referable to identical factors, there is accelerated destruction of the tubercle bacillus and increased resistance to infection. These relations are well illustrated by recent studies of Lurie. All that is known about human lesions of first infection and of reinfection indicates that man reacts to the tubercle bacillus like other susceptible mammalian species. There is little reason to doubt that the sensitization and increased resistance following infection are associated with increased injury caused by the tubercle bacillus and its products, intensified reaction to the presence of the microörganism, and, under favorable conditions, hastened destruction of the microörganism. Under unfavorable conditions, notably with infecting microörganisms in

overwhelming quantity, the disease progresses to a fatal end. It is noteworthy that in the late stages of pulmonary tuberculosis both sensitization and resistance diminish, and widely disseminated tuberculosis of larynx, intestine and internal organs may make its appearance.

Some observers have failed to find any significant relation between the results of experiments on lower animals and the complex changes that are found in association with human tuberculosis. Attempts, such as that of Ranke, to explain the pathogenesis of tuberculosis of man by reference to the imperfectly understood phenomena of sensitization or allergy have been conspicuously unfruitful and tend to retard objective investigation. Especially significant for the student of human pathology is the experimental observation that resistance against reinfection, though conspicuous, is not absolute and is overcome by increasing the reinfecting dose of tubercle bacilli. Moreover, both sensitization and resistance are temporary and disappear after complete healing of the lesion of first infection.

APICAL LESIONS OF FIRST INFECTION OR CHILDHOOD TYPE

No simple formula will explain the pathogenesis of tuberculosis in all of its varied manifestations. Tuberculosis of adult type usually has its origin in the apical or subapical part of the upper lobes of the lungs, whereas tuberculosis of children may occur in any part of the lungs, not more frequently in the apex than elsewhere. Caseous tuberculosis of adjacent lymph nodes is its characteristic feature. Unfortunately, with regard to its recognition during life, tuberculosis of first infection affects the apices with increasing frequency in adolescence and adult life. Some years ago I described an instance of apical tuberculosis in a negro woman 37 years of age with massive caseous tuberculosis of the regional lymph nodes, tuberculosis of the vertebrae, and death from generalized miliary tuberculosis. Some pathologists have regarded such apical lesions with caseous tuberculosis of adjacent lymph nodes as characteristic of the disease in adolescence, but Beitzke and others have denied this relation. In negro adults of Jamaica the writer has seen apical lesions of first infection accompanied by caseous tuberculosis of adjacent lymph nodes. In forty-four adult American negroes Everett found tuberculosis resembling that of white infants in nine instances; in thirteen instances the disease had similar characters, but evidently had had its origin near the apices of the lungs. In the remaining half of these lesions the disease had the character of the adult type of white persons. In twenty-one

instances of pulmonary tuberculosis in white persons examined for comparison all save two were of characteristically adult type. Of the two lesions of first infection or childhood type, with caseous tuberculosis of regional lymph nodes, one was basal and the other apical.

THE TUBERCULIN REACTION

In the period of life when tuberculosis is least severe and morbidity and mortality are at their lowest level, namely, between two and twelve years of age, the increment of new infections as shown by tuberculin tests and confirmed by observation made at autopsy is greatest. Muench has proposed to estimate this rate of increase by a catalytic curve fitted to the data defining the age incidence of the tuberculin reaction. From this curve the annual rate of increase of the reaction and the frequency with which the reaction is lost, or the reversion rate, are deducible. In a slum district of the city of Kingston, Jamaica (Wells), where tuberculous infection is widespread and approximately 80 per cent of children at the age of fifteen react to tuberculin, the rate of acquisition of the tuberculin reaction, Muench estimates, is with increasing age 16.51 per cent per year; in rural communities of Alabama, South Carolina and Florida (Aronson), the rate of increase is 5.72 per cent for white persons, of whom about 55 per cent react at the age of 15 years, and 6.72 per cent for colored, of whom 65 per cent react at 15 years of age. In rural counties of Michigan (Aronson) where tuberculous infection is scant and only 22 per cent have acquired the reaction at 15 years of age, the yearly rate of increase is only 2.61 per cent. This figure may be used as an index of the extent of tuberculous infection in a community.

In adolescence and early adult life the incidence of the reaction increases with age and even in the rural districts of Michigan it ultimately reaches 75 per cent at the age of 40 years (Aronson). In the larger cities of this country the frequency of infection after 25 years of age approximates 100 per cent. Adults usually react to 0.01 mgm. of tuberculin whereas in children 1 mgm. is often required to reveal the reaction. Where tuberculous infection is widespread, the sensitivity of adults is doubtless maintained by repeated infection with tubercle bacilli, and it is probable that these infections in most instances cause no recognizable lesion. With advanced age Aronson has found some diminution in the frequency of the tuberculin reaction and it is possible that this decrease is referable to less frequent contact with tubercle bacilli.

Calcified tuberculous foci have been found in approximately 5 per

cent of persons who failed to react to tuberculin (McPhedran and Opie). These lesions may be regarded as obsolete. A negative tuberculin reaction is evidence that there is no existing tuberculous infection. The few exceptions to this statement are readily recognizable because they are associated with obvious disease.

ASYMPTOMATIC OR LATENT LESIONS

Knowledge of tuberculous infection acquired in recent years by anatomical observation, tuberculin tests and roentgenographic examinations, has introduced some new aspects of the subject, not in accord with preëxisting convictions. Some clinicians have been loathe to admit the existence of significant tuberculous lesions unaccompanied by symptoms or physical signs. The application of the term latent to these lesions though supported by the authority of Laennec and others has been opposed by those who insist, contrary to accepted usage, that a demonstrable infection is not latent. These objections may perhaps be met in part at least by applying the term asymptomatic (F. F. Russell) to lesions that are unaccompanied by symptoms or physical signs. Their potential importance varies widely with their character and extent. In my experience calcified nodules have been followed by the adult type of tuberculosis only when there has been continued contact with tuberculosis. Since these lesions have little potential significance it is inadvisable to designate them by names that exaggerate their importance. The application of the term "childhood tuberculosis" with no further qualification to calcified nodules of lungs and lymph nodes has caused much confusion. Designation of them as "calcified nodules" or "calcified tuberculous nodules" is not ambiguous.

There is no evidence that children with calcified nodules of lungs or lymph nodes will be benefited by care in preventoria or open-air schools unless they are thus separated from contact with tuberculosis or have some condition not referable to tuberculosis.

The potential significance of asymptomatic or latent infiltrating lesions of childhood or of adult type varies with the character and extent of these lesions. An accurate definition of the frequency with which they become clinically manifest is one of the most important questions concerning the early recognition of tuberculosis. Soft or flocculent lesions may be distinguishable from those that are strand-like and presumably in process of healing. More information is needed concerning the fate of persons with asymptomatic or latent apical lesions. A large

part of the persons with these lesions when exposed to contact with tuberculosis develop clinically manifest disease after intervals of months or years, and the frequency with which this change occurs increases with the extent of the lesion (McPhedran and Opie). It occurs with greatest frequency in adolescence and early adult life and seldom after forty years of age. Latent lesions should not be identified with arrested tuberculosis since they have not passed through a period of clinically manifest disease.

A person with an asymptomatic or latent lesion that has been found to be progressive in successive radiographic films should receive the same care as one with clinically manifest disease.

Should the official registration of tuberculosis take cognizance of latent lesions? Practice in this relation will doubtless for a time vary widely and difficulties are numerous. A well-defined nomenclature is essential. Healed or healing lesions, such as calcified nodules of lungs or lymph nodes, strand-like pulmonary scars or scant salients projecting below the second rib, are so frequent and have such slight significance that their registration would have little value. Infiltrating lesions of childhood type or conspicuous latent apical lesions should, I believe, be recorded. Progressive latent or asymptomatic lesions should be registered, and, though separately classified, they should receive the same consideration from the standpoint of public health as clinically manifest disease.

EARLY DIAGNOSIS OF TUBERCULOSIS

Advance in the early diagnosis of tuberculosis is dependent upon its recognition before it has undermined health and manifested itself by symptoms or physical signs. How can grave asymptomatic or latent lesions be discovered by X-ray examination in persons who are presumably in good health? The periodic examination of healthy persons is a costly procedure and, save in a few isolated instances, is applicable only to selected groups. Observations made at the Henry Phipps Institute have shown that the repeated examination of persons in contact with tuberculosis may reveal from 10 to 20 per cent with manifest tuberculosis and 30 per cent or more with latent apical lesions. The radiographic examination of school children is costly, even when paper films are employed, and its value will vary with the frequency of the disease in the community. The tuberculin test will exclude infection in a considerable number of persons. Significant lesions are more likely

to be found in the adolescent children of high-schools and in the young adults of colleges and professional schools. Fellows has shown that the examination of applicants for industrial employment and of industrial employees may reveal a high incidence of persons with grave pulmonary lesions.

When with school-children or other groups of persons it is possible to obtain evidence of contact with tuberculosis the frequency with which lesions may be discovered by a limited number of examinations will be increased. Correlation between the medical inspection of school-children and the registration of tuberculosis might reveal at small cost a considerable number of children with advanced tuberculous lesions.

THE SPREAD OF TUBERCULOSIS

The spread of tuberculosis occurs in large part by long-drawn-out family or household epidemics in which the disease is slowly transmitted from one generation to the next. The tuberculin test shows that approximately 80 per cent of children of households in contact with persons with tubercle bacilli in the sputum have acquired infection within the first five years of life, but, in households in contact with a member with tuberculosis but with no discoverable tubercle bacilli in the sputum, only 30 per cent are infected. Roentgenographic examination of children exposed to tuberculosis shows that discoverable lesions appear more promptly in those who are exposed to open tuberculosis than in those exposed to tuberculosis with no tubercle bacilli in the sputum, and the preponderance is considerable in the early age-groups; but later the extent and character of lesions form a better index of the danger of exposure than the number of recognizable lesions.

During approximately eight years the progress of tuberculosis has been followed by Dr. McPhedran and the writer in one thousand families at the Henry Phipps Institute, and the time-relations between the appearance of the disease within the family and its transmission to other members of the household have been carefully recorded by means of appropriate graphs. From these graphs it is possible to determine with considerable accuracy the fate of persons exposed to the contagion of tuberculosis.

Life-tables may be used to show the annual frequency of manifest tuberculosis and of latent lesions and the death-rates from the disease at varying intervals after members of families come into contact with it. The fate of persons who have been in contact with tuberculosis varies

with their age at the beginning of exposure. Evidence may be quoted (Opie, McPhedran and Putnam) to show that in white persons first exposed between birth and nine years of age the annual frequency of tuberculosis in those living from twelve to fourteen years after the beginning of exposure is approximately 10 per cent, though many have already died from the disease. Among persons first exposed between ten and fourteen years of age the annual frequency of tuberculosis reaches 20 per cent. Among those first exposed after fifteen years of age the annual tuberculosis frequency reaches 10 per cent.

EXOGENOUS REINFECTION

An important question long under discussion is the source of the infection that occurs in adolescents and adults. Is it the continuation of an infection acquired in early childhood or a new infection? Pathological changes indicate that the lesion of first infection is encapsulated and healed at a time when the infection of adult life is progressive and there is no evidence that the latter spreads from the former.

In white persons first exposed to tuberculosis after fifteen years of age, pulmonary tuberculosis with few exceptions has the characters of the adult type. Since our life tables show that, in persons first in contact with tuberculosis after this age, the frequency of infection and of deaths from tuberculosis, like those of early childhood under corresponding conditions, increases rapidly and far exceeds the frequency of disease and death from tuberculosis in the general population, the adult type is evidently acquired by contact and is an exogenous infection of adolescence or adult life.

Prompt increase of clinically manifest tuberculosis and of deaths from tuberculosis following exposure to infection is even more conspicuous in the negro than in the white race, and occurs when age at the beginning of exposure varies from birth to nine years, from ten to fourteen years, or is more than fifteen years.

The application of roentgenographic methods to the recognition of tuberculosis of the lungs shows that the disease may be transmitted from husband or wife to the other marital partner. The earlier evidence of this marital transfer, it is well known, has been questioned by competent statisticians. More recently roentgenograpnically demonstrable lesions have been found in nearly half of those whose husband or wife has suffered with open tuberculosis (Opie and McPhedran), and this

figure so far exceeds that of adults with no marital exposure to the disease that its exogenous origin cannot be questioned.

EXTRA-FAMILIAL INFECTION

Increase in the incidence of infection with increasing age occurs with greatest rapidity in families exposed to contact with open tuberculosis, but even in presumably healthy school children with no known contact with tuberculosis it proceeds continuously, so that in cities like Philadelphia or New York approximately 80 per cent of children are infected at the age of fifteen years. In children with contact with open tuberculosis the annual increase with age of tuberculin reactions was approximately 21 per cent; with contact with tuberculosis with no discovered tubercle bacilli in the sputum, 10.9 per cent. In children with no known contact with tuberculosis the rate was 7.9 per cent; this infection is in large part extra-familial and the result of casual contact with the tubercle bacillus.

Do these infections, in large part acquired in early childhood, pursue in most instances a favorable course because the children are especially resistant at this time or because the number of infecting tubercle bacilli is small? The second explanation seems more probable, since with intimate contact with tubercle bacilli, such as occurs with familial exposure to tuberculosis, grave lesions are much more common during the same period of life.

INFLUENCE OF SEX ON TUBERCULOSIS

It is well known that the death-rate from tuberculosis in adolescent girls exceeds that of boys (*cf.* Putnam) and may reach a peak in early adult life, whereas the death-rate in the male sex rises continuously and exceeds that of women after twenty-five or thirty years of age. The familiar graph in which the death-rates for men, progressively increasing with age, exceed those of women in early adult life, is reproduced by the sex-age frequency of all tuberculous lesions and of lesions of adult type in members of families with tuberculosis under the care of the Henry Phipps Dispensary. It is noteworthy that this characteristic graph occurs in association with another infectious disease, namely, syphilis (Parran, Maxcy and Brumfield, etc.), and is best explained by the association of the sexes that begins at an earlier age in females than in males. Though the modes of transmission of tuberculosis and of syphilis have no similarity, marital tuberculosis and doubtless some extramarital in-

fections may be transmitted by intimate association of the two sexes. It is noteworthy that tuberculosis is with few exceptions acquired from adolescents or adults suffering with the disease. Since marriage occurs earlier in women than in men, and, in general, even in adolescence, girls tend to associate with boys older than themselves, disease transferred from one to the other would begin earlier in girls, but ultimately that of men would equal or exceed in frequency that of women.

THE FREQUENCY OF TUBERCULOSIS

Tuberculosis we know very well is no longer foremost among the causes of death, but it maintains its supremacy in adolescence and early adult life and is passed by heart disease, nephritis, cerebral haemorrhage and cancer, essentially diseases of later life, only after the fortieth year of life. Since death with increasing age must be regarded as inevitable, tuberculosis may still be regarded as our foremost public-health problem.

Of school-children examined in Philadelphia, six or seven per thousand had manifest pulmonary tuberculosis (Hetherington, Landis, McPhedran and Opie). Among young adults, male and female, including normal-school pupils, college students, law, dental and veterinary students, the incidence of unsuspected but clinically recognizable tuberculosis was two or three per thousand. The frequency of lesions of the apex of the lung, unaccompanied by symptoms or physical signs but of such extent that it reached from above to below the level of the clavicle, was considerably greater, namely, nine to twelve per thousand. These figures were exceeded by the medical students and graduate nurses that were examined.

Observations of much significance have been made by Fellows in New York City. By fluoroscopic examination of 14,000 persons applying for industrial employment, in great part young girls about eighteen years of age, he found 0.98 per cent with definite pulmonary tuberculosis, the majority of the cases being in his opinion clinically significant.

It is widely accepted, as the result of observations made on civil and military groups and confirmed by the Framingham Survey, that approximately one per cent of persons suffer with tuberculosis. If roentgenological examination is applied to adolescents and young adults who presumably have no tuberculosis, an additional one per cent are found to have apical lesions so advanced that they extend from above to below the clavicle.

A graphic record of the occurrence and spread of the disease in exposed households is an effective means by which the danger to the household and to the community may be evaluated. Such a graphic record of families or households under supervision shows who are actual and who potential sources of infection. It depicts the original source of infection and reveals its gradual spread. It provides a measure of the relative danger to which members of the family are subjected and can be used to determine how much medical and nursing care the family needs.

Detailed study of the progress of tuberculosis in families attending a tuberculosis clinic furnishes a measure of the adequacy of existing methods for control of the disease. The father of the family applies to the dispensary with a history of having had tuberculosis during a period of five or more years. In some instances his disease has been unrecognized and the first examination of the sputum demonstrates the presence of tubercle bacilli. It is probable that his wife and children have been living in contact with open tuberculosis more or less constantly during a considerable period of time, since all of them react intensely to minimal injections of tuberculin and most of them have tuberculous lesions demonstrable by X-ray examination. In such families children born during the period of contact have in many instances died from tuberculosis; children between the ages of three and twelve years usually escape grave disease, but adolescent children develop apical lesions which after a period of latency are associated with the familiar symptoms of chronic pulmonary tuberculosis and not infrequently with tubercle bacilli in the sputum.

In another group of families the existence of pulmonary tuberculosis with tubercle bacilli in the sputum in an adult member of the family has long been known and residence in a sanatorium has repeatedly separated him from the household. Nevertheless, a family graph will show that during the period of open tuberculosis the patient has been months or years with his family and in many instances he dies at home. The presence of conspicuous tuberculous lesions in children and often in adults of the family gives convincing evidence that transient segregation of the source of infection has not prevented household spread of the disease. Of thirty-seven persons with open tuberculosis chosen because they were members of families of considerable size, the sum of the time during which they were in contact with their families was thirty-two years and

of the time in which they were separated from these families in sanatoria or hospitals was twenty-nine years, that is, less than half of the sum of the periods of known dissemination of tubercle bacilli. This relation is an index of the efficiency of segregation and will vary widely in different places.

Summary and Rebuttal

This discussion concerning the relation of tuberculous infection to manifest disease and its application to the control of tuberculosis has shown that there is essential agreement upon some of the more important questions that have been considered. Tuberculosis is a widespread infection that in a small proportion of instances progresses to manifest disease, but, as Dr. Frost points out, the tubercle bacillus cannot spread unless it produces this effect. There has been no difference of opinion concerning the occurrence of a first infection and an adult type of tuberculosis but there is no general agreement concerning the criteria upon which this distinction can be made. What is regarded as the continuation of a first infection by one is regarded as adult infection by another. It is well recognized that the first infection or childhood type of tuberculosis may appear in adult life. Since the relation of the first infection to the adult type of disease is still under discussion it is inadvisable to designate the latter as reinfection.

There is uniformity of opinion concerning the benign character of tuberculosis in the period of childhood between two and ten years of age, when mortality is less than at any other period of life. The resolution of tuberculous lesions well illustrated by the clinical observations of Dr. Myers and the experimental studies of Dr. Medlar would have been questioned a few years ago. The calcified scars of lesions that fail to resolve have little potential significance and, when unassociated with more significant changes, require no special treatment.

A considerable part of this discussion has been concerned with the relation of the first infection or childhood type of tuberculosis to the adult type. The opinion that all tuberculosis is acquired in childhood is now abandoned, but there is no agreement concerning the relative frequency of endogenous and exogenous infection of adults. Anatomical evidence of the relation of the lesions of first infection to those of adult type, such as that presented by Dr. Sweany, will receive varied interpretation from pathologists.

Are those who have sustained a first infection more or less susceptible to a new infection? Since this important question has not been presented, I shall not discuss it.

Racial susceptibility has been discussed by Dr. Long. Experiments, such as those of Lewis, demonstrate that strains of animals obtained by selective breeding vary in their susceptibility to the disease. Tuberculosis of human races

is profoundly influenced by habits of life, crowding, poverty, and many other factors. Under primitive conditions the disease spreads rapidly in an agricultural or nomadic people that attempt to live in urban communities in contact with the tuberculosis of another race. It is probable that the effect of variations in the number of invading tubercle bacilli determined by habits, crowding, etc., must be defined before the significance of even more complex factors, such as heredity and nutrition, can be determined.

It is obviously desirable that every person be protected from contact with the tubercle bacillus. Even though it may not be possible to prevent infection wholly, diminution of the number of microörganisms that pass from the sick to the well will decrease the number of lesions that reach the level of manifest disease and become new sources of infection. There is as yet little prospect of a widely applicable immunizing agent that will effectively control the spread of this disease.

Tuberculosis is still the foremost public-health problem in many parts of this country and is the chief cause of death and disability in early adult life. Over vast areas of the Orient the disease is widespread and as yet unrestrained, and in many parts of the tropics it is a rapidly fatal disease that is increasing.

In many countries of Continental Europe the agencies for public-health and therapeutic control of tuberculosis are sharply separated, but in this country tuberculosis clinics combine the two functions. Though no decision concerning the relative merits of the two procedures is possible, significant aspects of epidemiology and prophylaxis may be overlooked by physicians interested chiefly in the treatment of the disease.

There are still some noteworthy defects in procedures directed to its control. Registration is notably defective and case-finding is only partially successful. Improvement in early diagnosis now depends upon the recognition of the disease in selected groups before tuberculous infection has produced symptoms and impaired health. Unfortunately, there is no exact information concerning the frequency of manifest disease and of potentially significant infection in different communities. It is noteworthy that in the larger cities of this country approximately one in fifty young adults have manifest disease or at least lesions that extend from above to below the level of the clavicle.

The success of the segregation of tuberculosis varies widely. The introduction into the routine of dispensaries maintained for the control and treatment of the disease of exact methods for studying the spread of infection in families would make it possible to adjust prophylactic care to the needs of each household and to determine how far access of tubercle bacilli to susceptible persons has been prevented.

FIRST-INFECTION-TYPE TUBERCULOSIS[1,2]

Its Treatment and Prognosis

J. ARTHUR MYERS, F. E. HARRINGTON, C. A. STEWART AND MARJORIE WULFF

What is the usual course of the disease produced by the first attack of tubercle bacilli upon the human body? Can the course of the lesions be modified by treatment? What is the immediate prognosis? What is the remote prognosis? These and other questions we believe have been answered by clinical observations at the Lymanhurst Health Center on the same children over a period of years; that is by a longitudinal study of a sufficiently large group of children so that the results are significant. Some of our children have been observed since 1921 and others have been added to the group in subsequent years.

In the beginning of our observations, we had considerable difficulty in arriving at definite diagnoses. The shadows of the tuberculous parenchymal lesions on the X-ray film were so homogeneous and often so large that they were frequently mistaken for pneumonia. Furthermore, there was much confusion in the literature at that time, since various workers had used such varied or no standard terminology in discussing these lesions. It was only through a period of observation that we were able to arrive at definite diagnoses in many cases. Indeed, after approximately fourteen years of observation on lesions of this type, we are forced to admit that, when they first make their appearance in macroscopic form, we are often unable to differentiate them from other conditions which result in similar shadows, such as the reinfection type of tuberculosis, pneumonia, etc. Therefore, a period of observation is still necessary in most cases. However, we have come to the conclusion that in the absence of significant symptoms, a lesion in the pneumonic stage which casts a shadow on the X-ray film that persists for one month

[1] Presented as part of a Joint Symposium on the topic, *Present Concepts of Tuberculous Infection and Disease: Their Principles and Application*, at the 31st annual meeting of the National Tuberculosis Association, Saranac Lake, New York, June 27, 1935.

[2] From the Lymanhurst Health Center and the Departments of Preventive Medicine and Internal Medicine, University of Minnesota, Minneapolis, Minnesota. Prepared with the aid of a grant from the Research Fund of the University of Minnesota.

or longer in the chest of a child who is sensitive to tuberculin is usually caused by tubercle bacilli. Whether the lesion is of the first-infection type or the reinfection type cannot then be determined without repeated studies over a long time except in the rather rare cases that are known by reason of previous periodic tuberculin testing to have recently become sensitive; hence, under these circumstances the present lesion can be identified usually as of the first-infection type. Another aid in differential diagnosis during childhood is the fact that the reinfection type of chronic pulmonary tuberculosis is quite rare under the age of ten or twelve years. If, after a long period of observation, the shadow present in a tuberculin-sensitive child gradually disappears, and at some subsequent time densities interpreted as calcium deposits appear at the sites of the previous pneumonic shadows or in the region of the lung hilum, or both, we feel very safe in regarding the lesion as representing the first-infection type of tuberculosis.

The pneumonic stage represents an early development in the course of the disease produced by the first attack of tubercle bacilli and is not a common finding because many children have passed through that stage before they are examined. Therefore, one must examine large numbers of children in order to collect a sufficient number of these cases to make a significant study. When school-children and preschool-children, who are positive tuberculin reactors have been examined, from 3 to 25 per cent have been reported to show evidence of the first-infection type of disease on the X-ray film. However, in most cases, calcium deposits in the hilum, Ghon tubercle-formation, etc., constitute the evidence, whereas a relatively small number are seen with the disease in the pneumonic stage. To date, we have found 206 children with the acute pneumonic type of primary tuberculosis which may be divided conveniently into three groups. In group I, we have presented 116 children whom we saw when the first-infection type of tuberculosis located in the lung parenchyma was in the pneumonic stage. Among the 116 children, there were 5 whose tuberculin tests and X-ray films were negative when they were first examined, but under observation the test became positive and later the parenchymal disease made its appearance. There were 3 others sensitive to tuberculin on first examination and the X-ray film showed no evidence of disease. On subsequent examinations, however, the parenchymal lesions made their appearance and followed the usual retrogressive course. From these and other observations, we have found that it may require some time after the tuberculin

test becomes positive before the lesion is sufficiently large and is of such a character as to cast a shadow which can be visualized on the X-ray film. In the group I children, we have kept the lesions under observation and have seen them reach the stage of calcification, either in the lung parenchyma, or in the lung hilum, or both; that is, sufficient calcium has been deposited to cast shadows which can be visualized on the X-ray film. After the parenchymal shadows have completely disappeared, there often remain alterations in the hilum shadows over a considerable period of time. These latter changes may gradually become less marked until the hilum shadow becomes normal, following which, evidence of calcium often makes its appearance.

The primary focus was located in the right upper lung field in 37 cases; in the left upper lung field in 24; in the right lower lung field in 22; in the left lower lung field in 9; in the middle portion of the right lung in 5. Primary foci in the lung parenchyma were bilateral in 7 cases, while in 12 there was parenchymal infiltration immediately adjacent to the hilum.

To group I must be added 5 children with parenchymal lesions present on first examination, which have disappeared, leaving only evidence of fibrous strands extending outward from the hilum toward the site of the original lesion. In these 5 cases, no evidence of calcium has yet appeared on the X-ray film.

In group II, there are 34 children who had definite changes in the lung hilum on first examination. In some of these cases, sharply outlined shadows were seen which were interpreted as enlarged lymph nodes and which encroached somewhat upon the lung parenchyma. In others, there was a general increase in size and density of the hilum shadows. In this group, the hilum changes were on the right side in 21, on the left side in 11, and bilateral in two. In none of them, on first examination, could definite evidence of a primary parenchymal focus be established, as in group I. Since hilum enlargement often remains for some time after the parenchymal shadows have disappeared when the latter changes are present on first examination, one cannot say with certainty that there has not been a primary parenchymal focus present which could have been clearly visualized a few months earlier had films been made at that time. In fact, in 12 of our 34 patients who had changes only in the hilum on first examination, definite evidence of Ghon tubercles was found subsequently. In this entire group of 34 children, calcium deposits later made their appearance in the hilum region.

The course of the disease was uniform in all children in groups I and II. When it was detected in the pneumonic stage, the shadows usually persisted for several months to a year or more. After a time there was disappearance of the shadow in the lung parenchyma, and at some later time, varying from months to a few years, deposits of calcium made their appearance in the parenchyma, in the hilum lymph nodes, or both, or fibrous strands remained. When changes were seen only in the lung hilum, calcium deposits later appeared in each case. These findings, then, constitute the answer to what is the usual course of the first-infection disease.

Throughout the entire evolution of the disease, significant symptoms were usually absent. A number of authors have reported fever, which nearly always begins at the time allergy appears, as a rather common symptom of the first-infection type of tuberculosis. The fever may last from a few days to several weeks. It may consist of only a slight elevation of temperature in some cases, while in others it may on occasions reach 104° or higher. One of us has seen in consultation a child with a definite first-infection type of tuberculosis in the pneumonic stage with a temperature of 105°. When such marked temperature elevation is present, we are inclined to believe that most cases are diagnosed as pneumonia. However, it appears that in the vast majority of cases that have temperature elevation, the symptom is not sufficiently marked to call the attention of the parents to it or to lead them to consider it as due to more than a common cold. It is quite possible that many of the children under our observation may have passed through such a mild febrile stage before we saw them. The extent of lesion, as manifested by shadows on X-ray films, which can exist without causing significant symptoms, and the length of time over which such large shadows persist, during which the children are apparently in perfect health, are nothing short of amazing. Recently we reëxamined all of the patients in groups I and II who could be traced, and talked with their parents regarding the children's past illnesses, present health, etc. When the parents were asked why the first examination was made which led to the detection of the disease, the answer nearly always was that a member of the family or some other close associate was found to have tuberculosis, following which the Minneapolis Health Department recommended the examination of all contacts regardless of the fact that they were apparently in perfect health. In fact, a history of significant symptoms was given in only two cases. This has been so consis-

tently true, that lack of significant symptoms is almost a diagnostic point.

Therefore, it is obvious that most of the children in groups I and II would not have been known to have tuberculosis had it not been for the family survey made because of contact exposure. In other words, these children would have developed their disease and brought it under control with no outward manifestations to make them aware of what was taking place, just as thousands of other children must have done.

The benignity of the lesions was met with such regularity and consistency as to convince us that the first-infection type of tuberculosis, even though it appears in a very young child and may reach considerable proportions, is not of itself a serious condition unless secondary complications arise as the result of endogenous superinfections or reinfections. Continued exposure to infection may play an important rôle in following the origin of complications.

Apparently only a relatively small number of the children who become infected with tubercle bacilli develop large lesions which can be located during life by our present crude methods of examination. In those who do present such lesions, we believe that the defense mechanism of the body has not adequately surrounded the foci of bacilli before allergy appears. We are inclined to believe that in the majority of cases, however, when the primary focus is located in the lung parenchyma but does not obtain roentgenographically demonstrable proportions, the defense mechanism of the body has the bacilli and the lesions they are producing so well surrounded that there is no excessive diffusion of tuberculoprotein into the adjacent tissues by the time allergy appears; therefore, there is little or no collateral inflammation, and the X-ray-film examination is not sufficiently refined to bring to light these lesions in the absence of collateral inflammation. Our evidence for such a statement is based upon observation when periodic X-ray-film examination did not reveal the location of the parenchymal lesion in cases which we have seen when negative to the tuberculin test but which later became sensitive to tuberculoprotein. However, many months or more than a year later in some of these cases, definite evidence of parenchymal calcium deposits made their appearance. This probably explains the fact that the X-ray-film examination of the chest is negative in such a high percentage of positive reactors. At this point, however, we must not overlook the fact that not all first-infection lesions develop in the lung but may appear in practically any part of the body, particularly the

abdomen, the throat, and the central nervous system. Most of these lesions, even though they develop areas of collateral inflammation, are not visualized during life, because we have no adequate method of detecting them. Moreover, they usually do not cause symptoms and, therefore, are not brought to physicians' attention. At some subsequent time, however, X-ray film through the cervical region, through the abdomen, etc., may reveal definite evidence of calcium deposits, and postmortem examinations may show such deposits in other parts of the body.

During the past six years, we have had opportunities to observe a considerable number of young adults, particularly those enrolled in schools of nursing and medicine who were previously negative to the tuberculin test but who became infected through exposure to tuberculous patients. Here we have found the course of the first-infection type of tuberculosis almost identical with that just described for children, thus disproving, in our opinion, the former belief that an adult who becomes infected for the first time nearly always develops rapidly progressive clinical tuberculosis.

In groups I and II, there are two Negro children and one Mexican child. The course of their first-infection type of disease did not differ from that of the white children. Among other Mexican and Negro children not reported in this paper, who already had Ghon tubercles present when we first saw them, there was no history of illness from tuberculosis and apparently they controlled the disease just as white children in the same community. This has also been found to be true of Indian children by one of us, as well as by other investigators, and still others have found that many Negro children react to the first attack of tubercle bacilli as do white children. Apparently the children of these races can bring primary tuberculosis under satisfactory control with approximately equal success.

Inasmuch as the first-infection type of tuberculosis, as already cited, is so benign among these children and among white adults, a question arises in our minds concerning the statement that the childhood or first-infection type of tuberculosis is very destructive among adult Negroes, Indians, Mexicans, etc. So far as we have been able to determine, statements made to this effect have not been based upon longitudinal studies of the same individuals; that is, we do not know what the antecedent history of allergy and infection has been. One must, therefore, ask the question whether most of these very destructive forms of tuberculosis

seen in certain races are not reinfections, rather than first infections? It is our belief that they are.

The question as to whether the course of the first-infection type of tuberculosis can be modified by any known form of treatment is in greatest need of clarification at the present time. The ultimate course of treatment affects large sums of tax-money and much preparation and work on the part of those engaged in the care of tuberculous children. That the answer has simplified and, in fact, almost negated the need for treatment of this type of disease was as much of a surprise to us as it must be to others, who, thinking in the terms of reinfection tuberculosis, feel that immediate treatment must of necessity modify the primary disease process in the child just as it does the reinfection type of disease in the adult. When our work began, we strongly recommended sanatorium care for every child who was found to have a focus of first-infection tuberculosis in the pneumonic stage. Many families refused to carry out our recommendations because there were no outward manifestations of tuberculosis. We then advised that their children who were old enough be admitted to the Lymanhurst School. Many even refused this for the same reason and insisted upon having their children remain at home with no treatment whatever. Thus, our children were divided into three groups, which have given us an unusual opportunity to observe the effects of treatment upon the first-infection type of disease. The first group consists of those whom we sent to sanatoria; the second, of those sent to a special school (Lymanhurst); and the third, of those who remained at home with no treatment except that every effort was made to break the contact when an open case of tuberculosis existed in the home or among other close associates. This same effort was exerted in all cases.

In fact, in groups I and II, consisting of 155 children who have been observed from the time the disease was in the acute inflammatory stage until lime or fibrous strands were deposited in sufficient quantity so that they could be visualized by the X-ray film, 19 were treated in sanatoria and 50 in the Lymanhurst School, while 86 remained in their homes. Of the 155 children, 136 were traced recently, while the remainder (11, no institution; 8, Lymanhurst) have moved away or for some other reasons could not be located at this time. Among the 136 traced, we are unable to see any difference in the course of the disease, regardless of whether the children were treated as strict bed-patients, were sent to a special school, or remained as active as any normal child is in its home.

In fact, with the exception of three who developed the reinfection type of disease (to be discussed later), the entire group traced in 1935 are apparently perfectly normal, healthy individuals, going about the activities of life just as other children in their communities who have not had tuberculosis. The first-infection type of tuberculosis in the pneumonic stage is rarely diagnosed when fever is present, except in the relatively few cases that have high temperature elevation. When the disease is detected in the febrile stage, it is only reasonable that the child should be treated just as when fever is caused by other infections, such as influenza. Since the febrile stage usually is of such short duration, the treatment can very well be carried out in the home, provided there are no uncontrolled sources of exposure among the associates, and other home conditions are good. The red-cell sedimentation rate has been found to be definitely elevated during the febrile stage, and some authors are strongly of the opinion that the treatment should be continued until the rate has returned to normal. However, the ultimate results in our cases have been equally good whether or not special treatment was administered. In no case have we resorted to collapse therapy in any form. At present, we can see no indication for such treatment. Therefore, the immediate prognosis of tuberculosis of the first-infection type among children and young adults is excellent, either in the absence or presence of treatment.

The ultimate prognosis with regard to tuberculosis, however, cannot yet be determined for this group of children until years have elapsed, because it will depend upon the number who later develop the reinfection and destructive type of disease either from endogenous or exogenous sources. It will also depend very much upon where this disease is located. If in the meninges or if bacilli are liberated from the old first-infection foci in large numbers into the blood-stream, diffuse meningitis or miliary disease will result. In fact, one child, not reported in groups I and II (but included in group III) because his lesions did not have time to calcify, had a typical first-infection type of lesion in the pneumonic stage in the left upper lobe in 1923, when he was only six months old. He was sent to a first-class sanatorium, where in approximately five months he was found to have tuberculosis of the left knee. Six months later, he died in the institution of tuberculous meningitis of endogenous origin caused doubtless by bacilli that escaped from preëxisting primary foci of disease.

In the case of another child, whom we first saw at the age of ten months

on February 19, 1934, the first-infection type of tuberculosis in the pneumonic stage was already well established in the left upper lobe. There was also definite evidence of disease throughout both lungs, which had somewhat the appearance of miliary disease. However, this child was not ill and her lesions were detected only through an examination made because of definite contact exposure. Unfortunately, in this case we do not know when her tissues first became sensitive to tuberculin, when the first-infection focus developed, or when the lesions we interpreted as miliary disease made their initial appearance. Suffice it, however, that this child without any serious illness began, after many months, to show evidence of clearing of the shadows interpreted as miliary disease. At present, these shadows have almost completely disappeared. We are now inclined to believe that the shadows we diagnosed as miliary disease were produced by bacilli of bronchogenic rather than haematogenous origin and that they were deposited and partially controlled presumably before allergy made its appearance. Throughout the course of the disease in this case, the first-infection pneumonic focus in the left upper lobe has shown the usual characteristics of such lesions, but, as yet, we are unable to detect any evidence of calcium either in the lung parenchyma or the regional lymph nodes. Meningitis and miliary disease, both reinfection forms of tuberculosis, may develop soon after the first-infection type of focus is laid down and the tissues have become allergic. However, they do not develop among infected infants with anything like the frequency that formerly was true, particularly if continued exposure to infection is prevented. Moreover, they do not develop in such a high percentage of infected infants as we formerly believed. This fact has been brought to light through the tuberculin test and subsequent observations.

Another reinfection type of tuberculosis, which more frequently occurs soon after the first infection type of disease is established, involves the pleura. In fact, in our group of 155 children, 26 have presented evidence of pleural involvement on the X-ray film examination. The evidence most frequently seen (18 cases) was that of residual thickening of the pleura over the greater part or all of the lung, so often observed after effusions have absorbed. In only 4 cases, however, did we see the children at the time when definite evidence of fluid was present.

The reinfection, chronic and destructive type of pulmonary tuberculosis usually does not make its appearance until the period of adolescence approaches and increases in frequency among positive tuberculin

reactors as age advances. However, there is the occasional exception. Even the infant may develop the reinfection type of pulmonary tuberculosis soon after the first infection is laid down, and in a short time cavities may appear and the disease may progress to a fatal termination. We are inclined to believe that many of the cases of this type reported in the literature have been erroneously considered as lesions of the first-infection type because they appeared at such an early age. Usually, the data have been incomplete in these instances: that is, the clinician or pathologist did not know when the child's tissues first became sensitive or how much exposure had taken place after allergy was present, etc. We have seen no such case among the very young children at Lymanhurst and attribute this observation in part to efforts made to prevent a continuance of exposure. However, two children among 136 traced in groups I and II have developed reinfection, chronic pulmonary tuberculosis which is far advanced in each case. One now is 18 years old and the other has passed the twentieth year. It is too early to make any statements concerning the ultimate prognosis among the remaining children of groups I and II, inasmuch as the average age of these children is only now twelve and one-half years: that is, they are just approaching the age when pulmonary tuberculosis of the reinfection type becomes prevalent.

However, we have had under observation for the same length of time another group of children who had the first-infection type of tuberculosis in the calcified stage when we first saw them; that is, on first examination Ghon tubercles were present or calcium had been deposited in the hilum region. In addition, we have observed another group who had the first-infection type tuberculosis as manifested by positive tuberculin reactions but who showed no X-ray evidence of lesions on first examination. When such groups were observed for approximately fourteen years or until the average age was about twenty-one years, we found that the clinical, reinfection type of tuberculosis had made its appearance much more frequently; in fact, more than five times as frequently among the children who were originally positive to the test as among those who were negative to the test on first examination. This seems to be very good evidence that the ultimate prognosis with regard to tuberculosis among children with the first-infection type is not particularly good since so many of them later develop reinfection types of the disease.

Clinical observation proved that any and all types of treatment do not affect the immediate prognosis of primary tuberculosis since the

disease is in itself benign. The crucial point is, however, the prevention of the reinfection type which is often decidedly not a benign condition. We have not been able to obtain any evidence to show that hospitalization, special schools, camps, or any other form of treatment except breaking contact with tubercle bacilli, has any particular influence upon the later development of reinfection type disease. In fact, our only fatal case died of tuberculous meningitis in a sanatorium after having been there many months and the two cases which later developed reinfection, chronic, pulmonary tuberculosis were given long periods of treatment in sanatoria for the first-infection type of disease when they were children. Our present evidence leads us to believe that approximately 20 per cent of children who react positively to the tuberculin test will at some subsequent time develop clinical, pulmonary tuberculosis of the reinfection type and that these catastrophies are spread over a wide range of years. Even if hospitalization of the child with the first-infection type of disease had proved beneficial, the problem would not be within the realm of physical possibility at the present time. It would mean hospitalization of all children with the first-infection type of disease over very long periods of time, since many do not fall ill from the reinfection type until the third decade of life or later.

We have under observation 51 children, group III, with lesions similar in every respect to those reported in groups I and II, but who have as yet shown no evidence of calcification on the X-ray-film examination. Six of these children have been observed for five or more years and their parenchymal lesions resolved in the usual slow manner. At the present time, there is no evidence of the previously existing shadows. In the remaining 45, the lesions have been observed a shorter period of time. While some have completely resolved, the majority of them are more recent cases which still have definite manifestations either in the lung parenchyma, the lung hilum, or both, but there is as yet no evidence of calcium deposits. Symptoms have been conspicuously absent. In each case the period of observation has been sufficiently long and the course of the disease so characteristic as to justify a definite diagnosis of the first-infection type tuberculosis. The cases of two of these children have been previously discussed: one died of meningitis and the other is apparently recovering from bronchogenic miliary disease.

In group IV are 58 children who had only one examination and for various reasons, such as moving away from the city and lack of coöperation on the part of parents, did not return for periodical examinations.

In all of these cases lesions were present, such as those described in groups I, II and III, and we are strongly of the opinion that a good many of them were due to the first-infection type of tuberculosis. However, it is impossible to diagnose with certainty from a single examination.

Originally Lymanhurst had wards, where children could be hospitalized. Observation, however, revealed the fact that there was no real necessity for such service and, therefore, the staff-members unanimously agreed that it should be discontinued. The school was retained as the treatment division, where children were carefully observed, but at the end of thirteen years of such observation the medical staff came to the conclusion that the child with the first-infection type of tuberculosis needs no special treatment, whether in a hospital or a special school, such as Lymanhurst. Although many staff-members had taken great pride in the school and were very desirous of having it continued, the actual facts convinced them that it was not necessary, and, therefore, they could not conscientiously ask that money derived from taxation be used for the maintenance of the treatment division. Thus, the medical staff recommended to the Director of Hygiene and the Commissioner of Health, and he in turn to the Board of Education and the Board of Public Welfare, that treatment of children with only the first-infection type tuberculosis be discontinued at Lymanhurst. This resulted in a false rumor now abroad that Lymanhurst has been closed. It is now a diagnostic and follow-up epidemiological centre.

Since the remote prognosis of the first-infection type of tuberculosis had been found to be poor because of development of reinfection-type disease, in about 10 per cent by the time the age of twenty-one years is reached, the staff strongly recommended that at least a part of the funds previously used in the operation of the treatment division of the institution be diverted to activities which observation had proved would yield the most in tuberculosis control; namely, bringing a larger number of children to the Out-patient Department to detect through the tuberculin test as many as possible who have been infected with tubercle bacilli; to carefully examine and follow such children and to put forth great effort to find the source of their infection through examination of their associates. The next procedure is to treat or isolate as many as possible of the clinical cases found among the associates. This, we believe, to be the best method of treating infected children of any community. It simply consists of breaking contact with the open cases of tuberculosis, giving those already infected a better chance to avoid the

reinfection type of disease, and preventing others from becoming infected.

All children reacting positively to the tuberculin test should have films made of the chest periodically, beginning at about the age of ten or twelve years. Experience has taught us that when chronic lesions of the reinfection type make their appearance in the lung, so as to be easily detected by the X-ray film, there is usually a long time, often two or more years, before symptoms develop. During this period most cases can be treated successfully, and many of them when adequately treated do not become open cases. We believe that it is far more economical and more satisfactory in every respect to keep the potential cases under close observation in their homes, and thus detect early the 10 to 20 per cent who will develop the reinfection type of disease than to provide treatment for first-infection type cases. The program at Lymanhurst has been one of observation and compilation of these observations. That these compilations run counter to the preconceived ideas now in vogue in no way invalidates them. As the series enlarges in number and length of time, the results can only be more staggering. We are well aware of the appeal that the needs of the tuberculous child makes to the general public, yet when that need is so clear-cut that observation and breaking of contact-exposure prove the answer, all available funds should then be diverted to that purpose. In conclusion, our observations lead us to believe that expenditure of funds to treat in hospitals, special schools, etc., the first-infection type of disease cannot influence its course; rather that observation for the appearance of the reinfection type and early treatment of that type is the only effective course now open to us in tuberculosis control.

THE OUTLOOK FOR THE ERADICATION OF TUBERCULOSIS[1]

WADE HAMPTON FROST[2]

Fifty years ago, in the light of Koch's discovery and of the whole germ theory of disease as it then stood, one of the great students of public health (1) could say, quite reasonably: "There is no theoretical reason why a purely contagious disease like tuberculosis may not be exterminated. If contagion can be prevented at all it can be prevented completely."

To-day extermination of an infectious disease does not appear so simple. This is especially true of the endemic diseases caused by obligate parasites of man transmitted directly from person to person by way of the respiratory tract. The obvious gaps in case-isolation, and the demonstrated high prevalence of carriers of certain pathogens have gradually forced the conclusion that environmental control, sufficient completely to prevent exposure to these directly transmitted infections, is beyond the range of what is practicable at present or can be foreseen. Experience is to the same effect. In general, the diseases of this group have shown no consistent, substantial decrease in recent years.[3] Diphtheria and scarlet fever have, indeed, declined greatly, but it is by no means certain that this has been due largely to environmental control. Their past history shows wide variations in prevalence and severity; and, in diphtheria, specific immunization and therapy have played a part.

Year by year, bacteriological, immunological and epidemiological observations have made it more plainly evident that the best modern environment sets no effective barrier against the common endemic infections transmitted directly by way of the respiratory tract. It is

[1] Presented as part of a Joint Symposium on the topic, *Present Concepts of Tuberculous Infection and Disease: Their Principles and Application*, at the 31st annual meeting of the National Tuberculosis Association, Saranac Lake, New York, June 27, 1935.

[2] Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland.

[3] In measles and whooping-cough, mortality may be substantially reduced by environmental improvements which tend to lower case-fatality without reduction in ultimate prevalence of the diseases. Hence the decline in mortality of these diseases in recent years does not imply corresponding decrease in morbidity.

demonstrable, in one way or another, that very few people escape infection, clinical or subclinical, and that escape from the diseases themselves must be credited more often to human resistance than to avoidance of exposure. Against such diseases specific immunization appears to be the logical method of attack, and smallpox, against which it has been applied, is the only disease of this group which has been regionally eradicated.[4]

The belief that it is practicable completely to prevent dissemination of infection transmitted from person to person by way of the respiratory tract is no longer tenable. Therefore, if the expectation of eradicating tuberculosis rests upon complete avoidance of infection, it must needs be abandoned for the present. However, the condition necessary for eradication of an obligate parasite is not that transmission be immediately and completely prevented, but that it be lowered and held permanently below the level at which a given number of infectious hosts succeed in establishing an equivalent number to carry on the succession. If, in successive periods, the number of infectious hosts is continuously reduced, and this declining ratio is continued long enough, extermination must be the result. Within historic times many species of animals have been exterminated, regionally or entirely, by man's intervention, throwing the biological balance against them, and it is not inherently improbable that the tubercle bacillus should be similarly exterminated as the result of human interference with its propagation.

It is true that the tubercle bacillus falls in that general group of pathogens against which environmental barriers are of least effect, namely, those which enter and escape by way of the respiratory tract; but it is differentiated from the other organisms of this group by an unusual combination of conditions limiting its propagation and rendering it peculiarly vulnerable to artificial interference. These conditions are, first, that in order to escape from its host it must cause a lesion which breaks through to the surface, and, second, that it succeeds in producing such lesions in only a limited proportion of infected persons.[5] Various other pathogens limited to the human host are subject to one or the other of these conditions, but not to both. For instance, the virus of

[4] An endemic infection may be considered eradicated from a region when it has ceased to be self-sustaining in the area and, on reintroduction, fails to become reëstablished.

[5] It is possible that tubercle bacilli may escape from apparently insignificant and supposedly closed lesions more frequently than is implied here. Present evidence would appear, however, to indicate that bacteriologically demonstrable open pulmonary lesions, discharging bacilli rather profusely, are the foci of predominant importance in general dissemination of the infection.

measles appears to be spread only from persons actually suffering from or in process of developing the eruptive disease; but it is so highly infective that it succeeds in producing this effect in nearly all persons who survive to adult age. On the other hand, the diphtheria bacillus, the pneumococcus, the virus of poliomyelitis and various other pathogens transmitted by way of the respiratory tract, cause clinical disease in only a small proportion of those who are infected; but actual disease is not essential to propagation of these microörganisms, since subclinical infections, being equally "open", suffice to spread them from host to host, and to perpetuate the species. The combination of the two limiting conditions is the peculiarity of tuberculosis.

This double restriction upon the propagation of the tubercle bacillus places it in a biological position analogous to that of certain lower animals which must produce enormous hordes of young in order to bring to maturity the much smaller number needed for perpetuation of the species. It implies that, in order to survive, the tubercle bacillus requires a *surplus*, perhaps a *very great surplus* of chances to establish infection. Conceivably the requisite level of transmission may be very high,—sufficient to provide, not merely universal exposure to infection, but frequently repeated exposures, with perhaps a high average dosage. Therefore, notwithstanding that case-isolation is obviously imperfect even to-day and that tuberculous infection is still very high in our large cities, these facts do not necessarily imply that existing environmental barriers are wholly ineffective against the tubercle bacillus. It is reasonable to suppose that such environmental improvements as are implied in more decent living,—better housing, personal cleanliness, avoidance of promiscuous spitting, etc.,—have been potent factors in forcing the steady decline of tuberculosis by diminishing exposure, even though they seem hardly to affect the prevalence of such infections as measles, whooping-cough and influenza. Also, it is of course quite obvious that, with all the difficulties involved, it is still possible greatly to diminish general exposure to the tubercle bacillus by earlier discovery and better isolation of open cases.

Tuberculosis also differs from the other directly transmitted respiratory tract infections in that its mortality has declined consistently for the last 50 years or more and continues to decline in every part of this country for which adequate statistics are available. It is not directly established by comparable statistical evidence that there has been a proportionate decrease in the prevalence of infective cases of the disease,

taking into consideration not only the number of cases but duration of the open stage. However, there appears to be no good reason to doubt that the prevalence of open lesions effective in spreading the tubercle bacillus has diminished progressively, and continues to diminish in each considerable period of time. If it be assumed, then, that environmental control affecting the spread of tubercle bacilli from existing foci can be indefinitely maintained at the present level, or improved, there are only two forces which, singly or together, would operate to check or reverse the downward trend of the disease, namely, (1) a decrease in mass resistance to the disease, or (2) some change in the fundamental adaptation of the tubercle bacillus to its human host, tending to promote survival of the parasite.

If the disease in question were measles, in the declining phase of an epidemic, it would be quite certain from past experience that the downward trend would eventually be reversed because of a lowering of host resistance. When a sufficient proportion of nonimmunes had been added to the population by birth or immigration, the average contact rate which had been ineffective against the highly immune population would suffice to produce an epidemic against the lowered mass resistance. With suitable modification, somewhat similar considerations apply more or less generally to the typical so-called epidemic diseases. Host-resistance, due to individual specific immunization, appears to be a factor of great importance in limiting the prevalence of such diseases and, by its lapse, to be of importance in determining the swing upward from a downward trend. The first question, therefore, is whether a similar reversion is to be expected in tuberculosis.

It is hardly to be doubted that progressively increasing human resistance has been a factor of importance in the decline of tuberculosis and that any serious loss of the resistance thus achieved would check the decline or reverse it. It is reasonable to believe, however, that a substantial part of the gain in mass resistance is permanent. Causes of importance in raising resistance to tuberculosis probably have been selective mortality and environmental improvements such as better nutrition and relief from physical stress, tending to raise what may be called nonspecific resistance. It is a reasonable expectation that the increase in average resistance due to these causes will be maintained, for, while complete elimination of the mortality from tuberculosis would check this process of raising genetic resistance, there is no apparent reason why it should result in reversion to a state of higher average

susceptibility than exists to-day. Also, any gains due to better nutrition and to other elements of personal hygiene should be permanent if civilization continues at its present level or a higher one.

The factor in human resistance which is of a less permanent order is individual specific immunization by so-called latent infection. At present a majority of the population in many areas acquire their first infections with the tubercle bacillus between late infancy and adolescence, precisely at the age when the immediate reaction to infection is most favorable to the host. The immunity thus conferred is perhaps not very durable, but it appears definitely to modify the course of the disease when it develops in later years. Further reduction in the prevalence of tubercle bacilli in the environment must necessarily postpone first infections to a later average age, and it is possible that at a certain stage this may prove disadvantageous; that primary infections in adolescence or adult life will produce open lesions more frequently than under present conditions, and that this will tend to increase mortality. The continued decline of adult mortality in areas of this country where the level of demonstrable childhood infection is already low would seem to indicate that eventual loss of mass immunity through postponement of first infection need not necessarily check the downward course of tuberculosis. However, the question has a crucial bearing on the outlook and requires thorough investigation. Fortunately, present conditions in this country are well adapted to extensive studies which should throw much light on the subject,—perhaps within a decade.[6]

The next question is whether it may be assumed that the specific properties of the tubercle bacillus have remained and will remain constant, leaving the rise and fall of tuberculosis to be governed *entirely* by the interplay of only *two* variables, namely, exposure to the tubercle bacillus and resistance to its effects. This is not necessarily so. It is, indeed, a legitimate inference from the general law of organic evolution that the tubercle bacillus has been and still is undergoing some sort of evolutionary change, tending to ensure its survival by better adaptation to man. It seems probable that the trend of evolution in the parasite is toward the production of open cases of longer duration, and probable, too, that it has kept pace with true evolutionary changes in the human host. It is not necessary, however, to suppose that this or any other

[6] If it should be clearly established that such immunization as is acquired naturally by latent infection in childhood affords enduring protection, artificial immunization offers possibilities for supplementary control which have not yet been fully explored.

change in the microörganism has been or will be rapid enough to ensure survival of the tubercle bacillus against the handicaps imposed by artificial interference with its propagation. Present knowledge is consistent with the view that the specific properties of the tubercle bacillus have not changed appreciably in modern times; and, in the absence of compelling evidence for measurable variation in the past, it is reasonable to expect relative stability in the future.[7] The possibility that the tubercle bacillus may, in the future, acquire quite different properties certainly introduces into future expectations an element of uncertainty, but the same may be said of the possibility that man may be unable to maintain control of his environment as effectively as at present.

In summary: The advance of knowledge and the cumulation of experience have revealed greater difficulties than were anticipated in the control of endemic infectious diseases transmitted directly from person to person by way of the respiratory tract. For most of these the hope of full and effective control except by specific immunization seems utterly remote. But tuberculosis may properly be regarded as an exception because of the apparent stability of the tubercle bacillus and the conditions limiting its escape from the human host; and the expectation of eradicating it by environmental control is as reasonable now as it was 50 years ago, though based upon different grounds. There are certain elements of doubt upon which light may be thrown by further systematic investigations along rather obvious and simple lines; for instance, more exact observations on the possible infectivity of apparently closed cases, and on the history, in adult life, of those who acquire and those who escape latent infection in childhood. There are other essential factors about which there can be no certainty except as revealed by the future course of events, namely, man's ability to maintain the present or a higher level of environmental control and the stability of the tubercle bacillus. Nevertheless, the expectation of indefinitely continuing decline is believed to be reasonable at the present time.

If the view which has been presented above is substantially correct, it carries the implication of a much more vigorous program of case-finding and isolation, with the definite objective of hastening eradication of the disease rather than merely maintaining partial control. How-

[7] The past history of certain epidemic diseases, notably diphtheria and poliomyelitis, suggests very strongly that within quite recent times their specific organisms may have developed more highly pathogenic properties; and, to the extent that this is indicated, the expectation of stability in the future is diminished.

ever, it is a grave matter to hold out to the public the expectation of eradicating such a disease as tuberculosis unless the expectation rests upon sufficiently solid ground. The ideas which are expressed here are presented, therefore, with the desire not that they be accepted but that they be examined critically and subjected to the searching test of matching this particular interpretation of tuberculosis against every item of available information. The question is of a kind which cannot be settled decisively except by long experience, but in the meantime it deserves, perhaps, freer discussion than it has had in recent years.

REFERENCE

(1) CHAPIN, C. V.: What changes has the acceptance of the germ theory made in measures for the prevention and treatment of consumption? Fiske Fund Prize Dissertation, no. 38, Providence Press Company, Providence, 1888, p. 44.

DIABETES AND TUBERCULOSIS

1. An Analysis of 80 Cases from the Standpoint of the Tuberculosis[1, 2]

GORDON B. MYERS AND RICHARD M. McKEAN

The association of tuberculosis and diabetes is frequent enough to provide a problem for anyone interested in the treatment of either disease. The vast literature on this combination of diseases has been thoroughly reviewed by Root (1), Banyai (2) and Scholz (3). Despite many favorable case-reports, most physicians specializing in the care of tuberculosis still look upon a coexisting diabetes with an attitude of resignation. This is well exemplified by the following quotation from Fishberg's book on tuberculosis, published in 1932 (4):

> Insulin is a dangerous therapeutic agent in tuberculous diabetics. In those with sclerotic or quiescent lung lesions, large doses of insulin are apt to reactivate the process and exudative lesions follow. In those with exudative or bronchopneumonic lesions, and in general in toxic cases, insulin is hardly of any value; even if the patient is rendered sugar free, the process in the lung pursues its course unabated.

Such an opinion was expressed by several members of the staff of the tuberculosis unit of the Herman Kiefer Hospital in August, 1929, when one of us (R. M. M.) undertook the supervision of the diabetic patients there. From August 1, 1929, to April 1, 1934, 80 patients presenting this combination of diseases were under observation for an average period of 514 days including an average hospital stay of 326 days (table 1). We are aware that this series is not large enough and has not been observed long enough to permit sweeping conclusions, but we believe that the results are sufficiently striking to justify a preliminary report.

Age: The age of onset of each disease is indicated in table 2. The tuberculosis became manifest after the age of 40 years in more than half of the cases of this series. The highest incidence was in the sixth decade,

[1] From the Tuberculosis Unit of the Herman Kiefer Hospital, Detroit, Michigan, and from the Department of Internal Medicine, Wayne University.

[2] Presented at a session of the Clinical Section at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May, 1934.

during which 21 cases made themselves clinically evident. Many authors have noted that the age distribution of diabetic tuberculosis parallels that of diabetes rather than that of tuberculosis in the general population. This is probably due to the fact that diabetes is usually

TABLE 1

Length of observation

LENGTH OF OBSERVATION	0–6 MONTHS	½–1 YEAR	1–2 YEARS	2–3 YEARS	3–4 YEARS	4+ YEARS
In hospital	39	15	13	10	2	1
After discharge	10	11	8	3	3	1

Average length of hospital stay	326 days
Average period of observation since discharge	188 days
Average total	514 days

	0–6 MONTHS	½–1 YEAR	1–2 YEARS	2–3 YEARS	3–4 YEARS	4+ YEARS	TOTAL
Total period of observation in hospital and after discharge	30	13	10	12	10	5	80
Alive	9	9	5	10	7	5	45
Dead	21	4	5	2	3	0	35

TABLE 2

Age of onset

	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+	TOTAL
Diabetes	0	9	14	21	16	17	2	1	80
Tuberculosis	0	7	13	16	18	21	4	1	80

TABLE 3

Known duration of diabetes and tuberculosis to April 1, 1934

	0–6 MONTHS	½–1 YEAR	1–2 YEARS	2–3 YEARS	3–5 YEARS	5–10 YEARS	10+ YEARS
Diabetes	6	8	6	6	18	26	10
Tuberculosis	8	16	15	11	22	8	0

the primary disease. In this series the diabetes antedated the tuberculosis in 52 out of the 55 cases in which the date of onset of clinical manifestations of each disease was known.

Duration: The known duration of each disease is given in table 3.

The diabetes has existed for 3 years or over in two-thirds of the cases, and the tuberculosis in more than one-third.

Sex and race: The sex distribution was about equal, there being 43 males and 37 females. Sixty-two of the patients were white and 18 colored.

Family history: Thirty-one had been in contact with active tuberculosis and 12 gave a positive family history of diabetes. Included in this group of 80 cases were 4 individuals in whom an immediate family history of both tuberculosis and diabetes was present.

SYMPTOMATOLOGY

Constitutional symptoms: The most frequent complaints were weakness and loss of weight, presumably because they are symptoms common to both diseases. Seventy-six of the patients (95 per cent) complained of weakness, and 69 (86 per cent) had lost more than 5 kg. (11 lbs.). The average weight loss prior to entry was 12 kg. (26.5 lbs.), and the maximum 55 kg. (121 lbs.). Only 25 (31 per cent) complained of anorexia. The preservation of the appetite in the remainder was probably due, at least in part, to the diabetes. Fifty-three (66 per cent) had had polydipsia and polyuria prior to entry, suggesting that the diabetes was grossly out of control.

The pulse during the first week in the hospital was below 80 in 4 cases; between 80 and 100 in 49, between 100 and 120 in 23, and above 120 in 4. Two of the 4 patients with an initial pulse-rate below 80 became steadily worse and died. The admission temperature was normal in 10. It was elevated 1° in 34, 2° in 22, 3° in 5, and 4° or more in 9. The average afternoon temperature for the entire period of hospitalization was between 97.8° and 98.6° in 42 cases, between 98.8° and 99.8° in 18, between 99.8° and 100.8° in 8, between 100.8° and 101.8° in 8, and above 101.8° in four. Night-sweats were among the presenting symptoms of 59 patients; in 18 of this group they were severe and drenching.

Local symptoms: Thirty-five patients (44 per cent) had had a severe cough prior to entry, and 36 (45 per cent) had had a mild but protracted one. In 9 (11 per cent) cough was negligible or absent. Thirty-one (40 per cent) had been expectorating profusely and an equal number moderately, prior to entry. In the remainder the sputum was scanty or absent. Twenty-six patients (32 per cent) gave a history of haemoptysis of 1 drachm or more, and 9 others (11 per cent) had gross pulmonary haemorrhages while in the hospital. Thirty-six patients (45 per cent)

had had pleurisy before admission, and 16 others (20 per cent) developed it while in the hospital. In several instances the pleurisy was a complication of surgical therapy. Spontaneous pneumothorax occurred in 2 cases. In one of these it followed artificial pneumothorax.

It is our impression that fever, night-sweats, productive cough, and, in particular, haemoptysis and pleurisy occurred about as frequently in this series as is nondiabetic tuberculosis. Likewise, the physical signs were in close accord with the X-ray findings in 81 per cent of the cases. Since the symptoms and signs of tuberculosis are so closely dependent upon the type and extent of the lesion, however, a much larger series of cases will be needed to conclusively determine the influence of a pre-existing diabetes.

The relatively high incidence of symptoms and pathognomonic signs in this series may be due to the fact that a large proportion of the cases were far advanced by the time that they reached the hospital. In the majority of cases the patient was responsible for the tardy diagnosis, through failure to consult a physician until his health was considerably undermined. In several instances the blame could be placed directly upon the physician. Constant watchfulness for the development of tuberculosis in diabetic patients cannot be too strongly emphasized.

Laboratory: The sputum was positive for tubercle bacilli in 76 cases (95 per cent). One of the four with negative sputum had a minimal pulmonary lesion. The other three had been transferred from other hospitals where positive sputa had been obtained previously. The sputum has become consistently negative in 7 of the 18 patients still in the hospital and was negative at discharge in 20 out of 35 cases.

Seventy-two patients showed glycosuria and hyperglycaemia on admission. The other 8 were transferred directly from other hospitals. The diabetes was eventually controlled in all cases.

The admission red blood count was above 4,000,000 in 57, between 3,500,000 and 4,000,000 in 18 cases, and between 3,000,000 and 3,500,000 in 5 cases. The haemoglobin exceeded 75 per cent in 52 cases and ranged from 65 to 75 per cent in 23, and from 55 to 65 per cent in 5 cases.

X-ray: Using the criteria adopted by the National Tuberculosis Association, the admission roentgenogram was classified as a minimal lesion in 3 cases (4 per cent), as moderately advanced in 14 (17 per cent), and as far advanced in 63 (79 per cent). The process was confined to the apex in 3 cases, to the subclavicular region in 10, and to the base of the lung in 2 cases. In the remainder the involvement was so extensive that

the point of origin could not be ascertained. Cavitation was demonstrable in 72 cases (90 per cent). The lesion was predominantly exudative in 24 cases (30 per cent), productive in 21 cases (26 per cent), and mixed in 35 (44 per cent). Nearly all of those classed as productive had a few exudative lesions as well. Apart from the fact that the proportion of mixed lesions was higher than in the nondiabetic we observed nothing roentgenographically distinctive of diabetic tuberculosis.

COMPLICATIONS AND ASSOCIATED DISEASES

Tuberculous: Twenty-seven patients developed pleural effusions as a complication of surgical therapy, including five with tuberculous empyema. Twenty-one patients had gastrointestinal symptoms suggesting tuberculous colitis (alternating diarrhoea and constipation, abdominal cramps, flatulence, nausea and vomiting). Since barium enemata were not a routine procedure, accurate statistics as to the incidence of colonic involvement are not available. Thirteen patients had laryngitis; while tuberculosis of the kidney was found in three patients, tuberculosis of the spine in two, and tuberculosis of the meninges, ribs, clavicle and mastoid bone in one each.

Diabetic: One patient was admitted in severe acidosis and lapsed into coma shortly afterward, from which she subsequently recovered. Several had been in coma prior to the onset of the tuberculosis. Seven patients had marked arteriosclerosis (cerebral, coronary and peripheral). Two of these had gangrene of the toes.

Associated diseases: The Wassermann reaction was positive in 8 cases (10 per cent). Five had moderate hypertension. Two had nodular goitre and slight hyperthyroidism. Two had pneumonoconiosis. One had pernicious anaemia.

TREATMENT OF TUBERCULOSIS

The routine medical treatment of tuberculosis was used exclusively in 26 patients (32 per cent) and was supplemented by collapse therapy in 54 (68 per cent). More than one type of collapse was attempted in 20 of the latter group. Unilateral pneumothorax alone was applied in 22 cases, bilateral pneumothorax in 2, and phrenic surgery in 10. Unilateral pneumothorax and phrenic surgery were used in conjunction in 16 cases, bilateral pneumothorax and unilateral phrenic surgery in 1, phrenic crushing and thoracoplasty in 1, pneumothorax, phrenicectomy and thoracoplasty in 1, and pneumothorax and pneumolysis in one.

TREATMENT OF DIABETES

In a separate communication (5) the composition of the diets, caloric requirements and insulin dosage of thirty-two of the group who were in the hospital for more than 6 months, and who coöperated fully at all times have been discussed at length. Let it suffice here to summarize briefly the salient features of the diabetic management.

The food was prepared and weighed in a separate kitchen under the supervision of a graduate dietitian. All food left on the trays after the meals were over was weighed and replaced by something with an identical glucose equivalent. Strict precautions were taken to prevent cheating on the diet. For these reasons it was felt that the diets prescribed for the patients were for the most part identical with those consumed.

The composition of the average diet served to these 32 patients was as follows: Carbohydrate 108 gm., protein 62 gm., and fat 162 gm. This yielded 2,138 calories, or an average of 34 calories per kilogram. In contrast to this, the average house-diet served to uncomplicated cases of tuberculosis contained from 300 to 350 gm. carbohydrate, 80 to 85 gm. protein and 120 to 150 gm. fat, yielding from 2,500 to 3,000 calories. Despite the fact that it was decidedly less nutritious than the average house-diet, the diabetic diet furnished sufficient calories to permit an average weight-gain of 7.4 kg. (16¼ lbs.), and to bring 24 of the patients up to or slightly above their standard weight, which was the desired goal. Six of the 8 patients who remained below standard weight are still in the hospital. A period of daily urinary nitrogen determinations were run on two patients receiving 0.8 gm. and 1.1 gm. protein per kg., respectively, and both were in positive nitrogen balance. In its relatively low protein and caloric content and in its relatively high proportion of fat to carbohydrate, the average diabetic diet served to these 32 patients was quite similar to the diet which McCann and Barr found to be most suitable in uncomplicated pulmonary tuberculosis (6). Since less pulmonary ventilation is required on such a diet than on the average house-diet, more rest is provided for the lungs.

The average amount of insulin needed to bring the patients under control on admission was 46 units daily, whereas 42 units was required at discharge. This does not give a correct impression of the changes in carbohydrate tolerance, since the average discharge diet contained considerably more available glucose than the average admission diet. Correcting for the excess available glucose on the hypothetical basis that 1 unit of insulin is equivalent to 2 gm. of glucose, a figure of 34 units

daily is obtained as the theoretical insulin requirement at discharge if the admission diet had been carried through.

RESULTS

Using the criteria adopted by the National Tuberculosis Association, the results to date (April 1, 1934) have been classified according to the type and extent of the lesion revealed by the admission X-ray in table 4. These data are not indicative of the final outcome, which cannot be predicted with certainty while the patient is still alive, because of the tendency for tuberculosis to become reactivated unexpectedly. We feel, however, that the patients have been observed over a long enough period to permit an estimate of the ultimate outcome. Therefore, a conservative prediction has been made and the anticipated results classified according to the extent of the lesion on entrance and according to the method of treatment in table 5.

TABLE 4

Results to date (April 1, 1934) classified according to type and extent of lesion on admission to hospital

		ARRESTED AND APPARENTLY ARRESTED	QUIESCENT	IMPROVED	UNTRACED	UNIMPROVED	DEAD	TOTAL	
I	Exudative	0	0	0	0	0	1	1	3
	Productive	0	0	0	1	0	1	2	
IIB	Exudative	2	1	1	0	0	0	4	13
	Productive	0	0	0	0	2	0	2	
	Mixed	1	2	2	0	1	1	7	
IIC	Exudative	0	0	0	0	0	1	1	1
IIIB	Exudative	3	0	2	1	2	3	11	44
	Productive	2	2	0	1	1	7	13	
	Mixed	6	1	2	0	5	6	20	
IIIC	Exudative	1	0	0	0	1	5	7	19
	Productive	1	0	0	0	0	3	4	
	Mixed	0	0	1	0	0	7	8	
Total		16	6	8	3	12	35	80	80

Influence of the type of lesion: An arrest or an apparent arrest was obtained in 25 per cent of the cases with exudative lesions, in 14 per cent

with productive lesions, and in 20 per cent with a mixed process. An eventual arrest is anticipated in a total of 42 per cent of the exudative, 29 per cent of the productive and 40 per cent of the mixed group.

Influence of extent of lesion: Twenty-one per cent of the 14 cases originally classed as moderately advanced have been arrested, and an additional 43 per cent will probably be brought to a standstill eventually. An arrest or an apparent arrest has been obtained in 25 per cent of the 44 cases in group IIIB. and is anticipated in another 16 per cent. Only

TABLE 5

Anticipated results classified according to method of treatment

ULTIMATE RESULT	ARREST OBTAINED OR ANTICIPATED				DOUBTFUL			DEATH OCCURRED OR ANTICIPATED					TOTAL
Admission classification	I	IIB	IIIB	IIIC	IIB	IIIB	IIIC	I	IIB	IIC	IIIB	IIIC	
Total cases	1	9	18	2	2	5	1	2	2	1	21	16	80
No collapse therapy	1	1	2	0	1	1	0	1	0	0	7	12	26
Collapse therapy used	0	8	16	2	1	4	1	1	2	1	14	4	54
Unilateral pneumothorax	0	2	7	0	1	1	0	0	1	1	7	2	22
Bilateral pneumothorax	0	0	2	0	0	0	0	0	0	0	0	0	2
Phrenic	0	3	1	1	0	1	0	0	0	0	2	2	10
Unilateral pneumothorax plus phrenic	0	1	5	1	0	1	1	1	1	0	5	0	16
Bilateral pneumothorax plus phrenic	0	0	1	0	0	0	0	0	0	0	0	0	1
Pneumothorax plus pneumolysis	0	0	0	0	0	1	0	0	0	0	0	0	1
Phrenic plus thoracoplasty	0	1	0	0	0	0	0	0	0	0	0	0	1
Pneumothorax plus phrenic plus thoracoplasty	0	1	0	0	0	0	0	0	0	0	0	0	1
Total	30				8			42					80

10 per cent of the 19 cases in class IIIC. have been arrested and no more are expected.

Influence of method of treatment: From table 5 it would appear that collapse therapy is far superior to exclusive medical treatment. Though this is probably true as a general rule, these data do not permit such a conclusion because the patients treated medically were, as a group, much further advanced than those treated surgically. Thus 16 out of the 20 deaths or expected deaths under exclusive medical treatment occurred in patients with lesions so far advanced that collapse was out

of the question; 2 deaths were the result of a transverse myelitis complicating Pott's disease, and only 2 might have been prevented if collapse therapy had been instituted. Both refused consent and left the hospital against advice. On the other hand, two patients with a far-advanced process have apparently become arrested on medical treatment alone.

In the 54 patients receiving collapse therapy, 22 deaths have occurred or are anticipated. Seven of these might have been averted if thoracoplasty had been done in addition to simpler methods of collapse therapy used. Operation was refused by two, and was considered inadvisable in the remainder because of the diabetes. Since then a 2- and a 3-stage thoracoplasty have been done in two moderately severe diabetics with no more reaction than occurs in uncomplicated tuberculosis. It is expected that this change in attitude toward thoracoplasty in the diabetic with tuberculosis will improve statistics in the future.

Arrested cases: The 16 patients classed as arrested or apparently arrested have been under observation for an average period of 462 days in the hospital and 639 days since discharge. All are ambulatory, are free from constitutional symptoms, and have negative sputum and X-ray findings of a stationary or retrogressive lesion. Three of the 6 men in the group are back at their former jobs, two expect to return soon, and one is leading a sedentary life at home. The 10 women are doing all or part of their housework; one has gone through pregnancy uneventfully.

Quiescent and improved cases: Four of the 6 patients with quiescent lesions are up and about the hospital; the other two were discharged recently. All 8 cases classified as improved were still in the hospital on April 1, 1934. An eventual arrest may be reasonably expected in all of the quiescent cases and in five of the 8 classed as improved.

Untraced: One of the 3 patients who have disappeared from observation had an apparently arrested minimal lesion when last seen in March, 1933. The other two had quiescent lesions when last seen in the summer of 1932. The outlook in one was very hopeful, and in the other dubious.

Unimproved cases: Seven of the 12 patients classified as unimproved were still in the hospital on April 1st, but in each the prognosis is very poor. These are distributed as follows: (IIB, 1; IIIB, 5; IIIC, 1). The outlook in two others is doubtful. Two (both of class IIB) did not remain in the hospital long enough for any appreciable change to occur. With proper coöperation an eventual arrest would be expected in both. The twelfth patient in this group was classified in group IIIB on his

admission in April, 1930, and was considered apparently arrested at discharge exactly three years later. He then disappeared from observation, discontinued his insulin, and did not follow his diet. He returned in March, 1934, with an acute exudative process in both lungs. This case illustrates the necessity for careful diabetic control even after the pulmonary process has apparently become arrested.

Cause of death: Twenty-seven patients expired in the hospital and eight have died since discharge. Of these thirty-five, pulmonary tuberculosis was the principal cause of death in thirty-one. Twenty-one of this group died of what is loosely termed toxaemia. One died suddenly of massive pulmonary haemorrhage; four others died following repeated haemoptyses. Two died as a result of tuberculous empyema. Another died suddenly at home, apparently of spontaneous pneumothorax on the relatively less affected side. A further patient, who was very dyspnoeic as a result of a pleural effusion, expired suddenly during an attempted aspiration. The last patient of this group had had a productive left apical lesion for 6 years and was admitted because of increasing dyspnoea, cyanosis and peripheral oedema. The pulmonary involvement was not sufficient to account for the symptoms and the heart was considered negative by three cardiologists, except for right ventricular preponderance in the electrocardiogram. The patient ran a downhill course and eventually died with signs of right heart failure. At autopsy a band of adhesions was found arising from the left upper lobe and compressing the pulmonary artery.

All but two of the 31 patients who died of pulmonary tuberculosis were classed as far advanced on admission. One of these, who had been placed in class IIC, died of tuberculous empyema and chronic nephritis. The other, originally in class I, left the hospital against advice, did not follow instructions at home, and on readmission had a far-advanced process.

Two of the patients died of transverse myelitis secondary to Pott's disease. One of these had a minimal, the other a far advanced pulmonary process. Another, whose moderately advanced pulmonary lesion was apparently improving, developed a tuberculous meningitis which proved fatal. The last death occurred in a patient who had been under observation at home for nearly two years since his discharge in March, 1932, and was considered an arrested case. He had been working in a brewery, had a retrogressive pulmonary lesion, a negative sputum, and was symptom-free until February 5, 1934, when he was taken with a chill, followed by sustained fever, cough and rusty sputum, and died one week later. He was attended by his family physician, who found evidence of

gross consolidation in his previously less affected lung, and made a diagnosis of lobar pneumonia. This was the logical diagnosis from the clinical picture, though an acute pneumonic tuberculosis cannot be excluded since X-ray and sputum examinations were not made.

Contributory causes of death: Arteriosclerosis was considered a contributory cause of death in 4, chronic nephritis in one, and pernicious anaemia in one. Three moribund patients died in insulin reactions. In each case it was felt that the reaction merely precipitated a death that was inevitable. Severe insulin reactions occurred in many whose strength was slightly or moderately impaired without threatening life. None of those who died in the hospital was in an appreciable degree of acidosis at death.

EFFECT OF DIABETES UPON TUBERCULOSIS

Uncontrolled diabetes: Eight out of 10 patients who neglected treatment of their diabetes after discharge from the hospital have returned with fresh exudative lesions. On the other hand, there was a steady improvement in the pulmonary process in two patients who had a persistent hyperglycaemia but showed no glycosuria or acidosis. It would thus appear that the tuberculosis generally becomes worse when the diabetes is grossly out of control but may show improvement when the urine is kept free of glucose and acetone bodies, even though the blood-sugar remains elevated.

Controlled diabetes: To determine the effect of controlled diabetes upon the course of tuberculosis it is necessary to compare the end-results in carefully treated diabetic tuberculosis with those in uncomplicated tuberculosis of similar extent and severity at the time therapy was instituted. Since there is no precise method of evaluating either the extent or severity of the pulmonary process on admission or the response to treatment, a large group of cases is needed to minimize errors of judgment. It will probably take several more years for a sufficiently large series of cases of diabetic tuberculosis to accumulate in any one clinic. Meanwhile, statistics of various authors must be combined to form a basis for conclusions (as to the effect of diabetes upon tuberculosis) and therefore ours are reported at this time.

The classification of the National Tuberculosis Association was used in evaluating the extent and severity of the lesion on admission. Since practically all of the diabetics fell into groups IIB, IIIB or IIIC, only the nondiabetics classified on entry into one of these three groups were con-

sidered. The results in all patients originally in one of these three groups and discharged during the years 1929–1933 inclusive were classified as improved, unimproved or dead, and were compiled in table 6. In spite of the disparity in total number of cases in the diabetic and nondiabetic groups, a striking similarity in the percentage of improved, unimproved and dead is evident. Since many patients were moribund on admission and since many others did not remain under treatment long enough to expect any change, another table was made in which only those patients

TABLE 6

Comparison of results in diabetic and nondiabetic tuberculosis

Condition at discharge of all patients leaving hospital in the period 1929–1933 inclusive

CLASSIFICATION ON ADMISSION	NONDIABETIC TUBERCULOSIS				DIABETIC TUBERCULOSIS			
	Total cases	Improved	Unimproved	Dead	Total cases	Improved	Unimproved	Dead
		per cent	*per cent*	*per cent*		*per cent*	*per cent*	*per cent*
IIB	805 (19%)	78.1	16.8	5.1	5 (8.1%)	80	0	20
IIIB	2,301 (54.3%)	54.7	26.3	19	40 (64.5%)	65	10	25
IIIC	1,131 (26.7%)	3.4	12.3	84.3	17 (27.4%)	11.8	17.6	70.6
Total	4,237	46.7	19.5	33.8	62	51.6	11.3	37.1

TABLE 7

Condition at discharge of all patients in hospital over 180 days (1929–1933 inclusive)

CLASSIFICATION ON ADMISSION	NONDIABETIC TUBERCULOSIS				DIABETIC TUBERCULOSIS			
	Total cases	Improved	Unimproved	Dead	Total cases	Improved	Unimproved	Dead
		per cent	*per cent*	*per cent*		*per cent*	*per cent*	*per cent*
IIB	239 (18.5%)	89.2	6.2	4.6	1 (3%)	100	0	0
IIIB	895 (69.4%)	63.2	14.2	20.6	22 (82.2%)	77.3	4.5	18.2
IIIC	155 (12.1%)	15.5	13.5	71	4 (14.8%)	50	0	50
Total	1,289	64	12.5	23.5	27	74.1	2.7	22.2

in the hospital over 180 days were included (table 7). Slightly better results were obtained in the diabetic in the sanatorium for more than six months than in the nondiabetic.

If a statement based on so few cases may be ventured, it would appear that, as long as the diabetes is controlled, the tuberculous patient with diabetes does at least as well as the one without diabetes and may improve more rapidly, owing to the fact that less pulmonary ventilation is required with the usual diabetic diet than with the ordinary house-diet.

SUMMARY AND CONCLUSIONS

1. This study is based upon a group of 80 patients with coexisting diabetes and tuberculosis, who were under observation for an average period of 514 days, including an average hospital stay of 326 days.

2. The tuberculosis became manifest after the age of 40 years in more than half of the cases, the highest incidence being in the 6th decade.

3. Thirty-two per cent gave a history of gross haemoptysis, whereas 45 per cent had had pleurisy prior to entry. The admission sputum was positive in 95 per cent of the cases.

4. The tuberculosis was classified as minimal in 4 per cent of the cases, as moderately advanced in 17 per cent, as far-advanced B in 55 per cent and as far-advanced C in 24 per cent. The lesion was predominantly exudative in 30 per cent, productive in 26 per cent and mixed in 44 per cent. Cavitation was demonstrable in 90 per cent.

5. The composition of the average diet of 32 patients in the hospital over 6 months was as follows: carbohydrate 108 gm., protein 62 gm., fat 162 gm. This yielded 2,138 calories and was sufficient to permit an average weight gain of 7.4 kg. (16.25 lbs.). The average amount of insulin required for diabetic control was 46 units daily on admission and 42 units daily at discharge.

6. The routine medical treatment of tuberculosis was used exclusively in 32 per cent of the cases, and was supplemented by collapse therapy in 68 per cent. Unilateral pneumothorax was induced in 39 patients and bilateral pneumothorax in 3; while phrenic-nerve surgery was performed in 28 cases, and thoracoplasty in 2.

7. Thirty-five of the 80 patients are dead. Pulmonary tuberculosis was the principal cause in 31, Pott's disease in 2, tuberculous meningitis in one and lobar pneumonia in one.

8. An arrest or an apparent arrest was obtained in 21 per cent of the moderately advanced cases, in 25 per cent of those in class IIIB, and in 10 per cent of those in class IIIC. An eventual arrest is anticipated in an additional 43 per cent of class II and in another 16 per cent of class IIIB.

9. The results in this group of cases of diabetic tuberculosis compare very favorably with the results obtained at this hospital in nondiabetic tuberculosis of like severity. It would thus appear that, as long as the diet and insulin are carefully regulated, a coexisting diabetes does not have an adverse effect upon the course of pulmonary tuberculosis.

We wish to acknowledge our indebtedness to Dr. Samuel S. Altshuler for his aid in diabetic management, to the Superintendent of Herman Kiefer Hospital, Mr. George Phillips, and to the medical, surgical and dietetic staffs of the Tuberculosis Unit for their splendid coöperation.

REFERENCES

(1) ROOT, H. F.: Association of diabetes and tuberculosis, New England J. Med., 1934 ccx, p. 1, 78, 127 & 192.

(2) BANYAI, A. L.: Diabetes and pulmonary tuberculosis, Amer. Rev. Tuberc., 1931, xxiv, 650.

(3) SCHOLZ, K.: Diabetes mellitus und Lungentuberkulose, Ztschr Tuberk., 1931, lxi, 129.

(4) FISHBERG, M.: Pulmonary tuberculosis, ed. 4, 1932, ii, p. 214.

(5) MCKEAN, R. M., AND MYERS, G. B.: The metabolic aspect of associated diabetes mellitus and pulmonary tuberculosis, Ann. Int. Med., 1935, viii, 1591.

(6) MCCANN, W. S., AND BARR, D. P.: The metabolism in tuberculosis, Arch. Int. Med., 1920, xxvi, 663.

MCCANN, W. S.: The effect of ingestion of food stuffs on the respiratory exchange in pulmonary tuberculosis, Ibid., 1921, xxviii, 847.

EXPERIMENTAL DIABETES AND TUBERCULOSIS IN THE DOG[1,2]

M. MAXIM STEINBACH, SIDNEY J. KLEIN AND MAURICE DESKOWITZ

For a long time it has been believed that diabetes predisposes human beings to infections, including tuberculosis, and that when a diabetic individual develops tuberculosis the latter disease is severe and often fatal. Moreover, the diabetic usually becomes tuberculous at a period of life when the mortality peak from tuberculosis for the average population has declined. The highest mortality rate from tuberculosis in females is in the age-period from 25 to 35 years, and in males from 35 to 45; whereas the average age for the development of diabetes is 51, and for diabetic mortality *per se* the average age is 61.2, a period of life less commonly attained by the tuberculous patient (Root). In spite of the fact that the death-rate from tuberculosis has decreased so radically in the past 50 years, and that this has naturally tended to reduce the number of contacts for the diabetic, the incidence of tuberculosis among diabetics remains high. Of course, the number of tuberculous diabetics has increased in the past few years, in part, because there are more people living to-day at the diabetic age, and the duration of life of the diabetic has been increased, and therefore there is greater opportunity for the infection of diabetics by the tubercle bacillus, as well as for the activation of old dormant or obsolescent tuberculous foci in diabetics.

The high incidence of tuberculosis among diabetics has been appreciated for a long time. Thus, Windle found at autopsy that 50 per cent of his 355 diabetics had active tuberculosis, and Croner reported 37 out of 100. Banyai, who collected from the literature 8,520 diabetic cases, found that the incidence of tuberculosis was 2.6 per cent, or three times as great as among the general population. According to Root also, the incidence of pulmonary tuberculosis in the adult diabetic is two or three times that in the nondiabetic of the same age group. Root further states that the incidence among diabetic children before the age of 15 is thirteen

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times that of normal children: thus, among 140,000 school children the incidence of tuberculosis was 0.12 per cent, while the incidence among 750 diabetic children of the same age-period was 1.6 per cent. Among adolescent diabetics between the ages of 15 and 19 inclusive, pulmonary tuberculosis occurred sixteen times as frequently as among nondiabetic high-school children.

Tuberculosis in the diabetic is rapidly fatal, as was shown by Fitz, who found that 63 per cent of his cases died in less than one year (19 of 31 cases). While many observers agree with the findings of Fitz, there are those who feel that the prognosis when these two diseases coexist is not necessarily unfavorable (Joslin; Rosenberg and Wolf).

An experimental approach to this problem requires a consideration of the following question: If diabetes increases susceptibility to tuberculosis, is it because the metabolic disturbance enhances the multiplication of the tubercle bacillus in the infected host, or does diabetes merely lower the host's general resistance? It is of interest to note in this connection that Long and Vorwald found that feeding albino rats infected with tubercle bacilli on a diet to which glycerol was added, or injecting glycerol into the circulation, enhanced the multiplication of tubercle bacilli in the host. It is well recognized that when glycerol is added to a diet or is injected into the vascular system, it is converted into glucose. *In vitro*, the growth of the tubercle bacillus is definitely enhanced by the addition of either glycerol or glucose to the medium.

In this study we have attempted to determine whether it was possible to reproduce in the experimental animal a condition similar to that which occurs in the human diabetic, that is, an increased susceptibility to tuberculosis. This was necessary before proceeding to determine the actual factors responsible for the lowered resistance. For this experiment it was necessary to choose an animal refractory to tuberculosis, remove the pancreas *in toto*, produce diabetes, and subsequently infect the animal with tubercle bacilli. We chose the dog because this animal is recognized as possessing a high resistance to mammalian and avian tubercle bacilli.

In a previous communication (Steinbach and Deskowitz) we reported the production of tuberculosis in diabetic dogs. In that series of 8 pancreatectomized dogs, seven became severely diabetic. The blood-sugar varied from 292 to 399 mgm. per 100 cc., while the average for all 8 dogs was 312 mgm. per cent. The 8 animals were subsequently injected intraperitoneally with a human strain of tubercle bacilli (H37) in a dose

of 1 mgm. per pound body-weight. Six of the 7 diabetic dogs developed tuberculosis. These animals were autopsied at from 29 to 95 days after infection. The lungs and the liver were the organs chiefly involved; the spleen was never affected. Caseation was found only once, and then in the retroperitoneal lymph nodes. One of the 7 diabetic dogs was negative for tuberculosis. The eighth dog developed only temporary diabetes and mild tuberculosis. This animal, and two pancreatectomized dogs with temporary diabetes which were still living at the time of our previous communication, will be discussed later in this paper (see table 2). The experiment was controlled with 8 animals. These controls were laparotomized and closed without interference with the pancreas, and were infected 24 hours after operation with the same strain (H37), by the same route, and with a similar dose. Microscopic examination failed to reveal tuberculosis in any of these control dogs.

We report here the results in another series of dogs that were pancreatectomized and infected with tubercle bacilli. The strain used (B1) was more virulent than that used in the previous series, and a more vulnerable route of injection (intravenous) was employed. The results afford further confirmation of our previously reported finding that pancreatectomy, when resulting in diabetes, lowers the resistance of dogs to tuberculosis. Moreover, evidence has been obtained which would indicate that this lowering of resistance in the dog is associated with faulty carbohydrate metabolism.

Our recent series included 5 pancreatectomized and 3 control dogs (see tables 1 and 2). The animals were all young and healthy. They were weighed and tuberculin-tested, and the urine and blood were examined for glucose. The urine was tested for reducing sugar by the Benedict method, and for acetone bodies by the sodium-nitroprusside method. The blood-sugars of all the dogs before operation were found to vary from 80 to 122 mgm. per cent. All the animals were operated upon under ether anaesthesia. Five of them were pancreatectomized; and the 3 control dogs were subjected to laparotomy and closed without injuring the pancreas. Twenty-four hours after the operation, the pancreatectomized and the control dogs were inoculated intravenously with a virulent bovine strain of tubercle bacillus (B1), in doses of 1 mgm. per pound body-weight. At this time the blood-sugars and urinary sugars and acetone bodies were again determined, and these tests were carried out at least weekly thereafter. No positive sodium-nitroprusside tests were obtained in this second series, due perhaps to the short period of survival

of the pancreatectomized animals. However, in the first series previously reported, acetone bodies were occasionally encountered in the

TABLE 1

Increased susceptibility of pancreatectomized diabetic dogs to the tubercle bacillus

DIABETIC ANIMALS (PANCREATECTOMIZED AND INFECTED)						CONTROL ANIMALS (LAPAROTOMIZED AND INFECTED)					
Number	Body-Weight (kg.) Preoperative	Body-Weight (kg.) Antemortem	Days Lived Postinfection	Average Blood-Sugar, mgm. per cent	Microscopic Pathology	Number	Body-Weight (kg.) Preoperative	Body-Weight (kg.) Antemortem	Days Lived Postinfection	Average Blood-Sugar, mgm. per cent	Microscopic Pathology
102	15.5	10.5	D25	250	Lung 4+ Kidney 4+ Liver 4+ Omentum 2+ Diaphragm 4+	101	16.5	13.5	K44	92	Liver 3+
139	6.3	4.0	D17	298	Liver 4+	103	13.8	12.2	K44	86	Kidney 1+
107	14.4	13.2	D14	303	Kidney 1+ Diaphragm 1+	120	13.0	12.5	K34	104	All organs negative

All animals inoculated intravenously with bovine tubercle bacilli (B1), 1 mgm. per pound body-weight.

The degree of involvement is indicated by plus signs, from 1+ to 4+.

D = Died. K = Killed.

TABLE 2

Susceptibility of pancreatectomized dogs with temporary glycosuria and hyperglycaemia to the tubercle bacillus

NUMBER	BODY-WEIGHT (KG.) Preoperative	BODY-WEIGHT (KG.) Antemortem	DAYS LIVED POSTINFECTION	AVERAGE BLOOD-SUGAR (MGM. PER CENT)	MICROSCOPIC PATHOLOGY
680*	11.2	8.2	D16	130	Lung, liver, kidney, mesenteric nodes positive
607*	15.0	10.5	D124	117	All organs negative
684*	12.8	10.0	K316	116	All organs negative
106†	12.7	9.3	K25	112	All organs negative
105†	18.2	12.0	D32	180	All organs negative

* Animals inoculated intraperitoneally with human tubercle bacilli (H37), 1 mgm. per pound body-weight.

† Animals inoculated intravenously with bovine tubercle bacilli (B1), 1 mgm. per pound body-weight.

D = Died. K = Killed.

urine of those dogs suffering from severe diabetes. Small doses of insulin (5 to 15 units) were administered daily to the pancreatectomized animals

after feeding, to offset coma and prolong life. This dose of insulin never reduced the blood-sugar below 250 mgm. per cent. To replace some of the digestive enzymes of which the pancreatectomized animals were deprived, desiccated pancreatic substance or fresh pancreas was incorporated in their food.

Three of the 5 pancreatectomized dogs developed severe diabetes. They survived only for a relatively short period (14, 17 and 25 days); this we attribute, in part, to the unusually hot July weather which prevailed at the time of the experiment. The control dogs were killed after a somewhat longer interval (34 or 44 days). We found that the pancreatectomized diabetic dogs showed severe tuberculosis, involving many organs. Two of the 3 control dogs also developed tuberculosis; one had moderate infiltration of the liver, and the other had a few epithelioid tubercles in the kidney.

In detail, our findings were as follows:

Pancreatectomized dog 107 lived 14 days. Three days after operation the blood-sugar was 308 mgm.; 4 days later it was 298 mgm. per cent. The urine showed 3+ sugar 6 days after operation. Autopsy revealed early tubercles in the lung and liver. Microscopic studies of these tubercles showed them to be composed mainly of epithelioid cells. Control dog 120, killed after 34 days, failed to reveal any evidence of tuberculosis.

Pancreatectomized dog 139 lived 17 days. Four days after operation the blood-sugar was 256 mgm.; 10 days later it was 340 mgm., giving an average of 298 mgm. per cent. The urine showed 3+ a week after operation, and 3 days before death it was 4+. Autopsy showed extensive tuberculosis in the liver, and moderate involvement of the lungs; whereas control animal 103, killed after 44 days, showed only a few tubercles in the kidneys, the rest of the organs being negative. Although one would not expect to find very extensive disease 14 and 17 days after infection, these two pancreatectomized diabetic animals demonstrated a precocious development of tuberculosis.

Our most significant findings were with pancreatectomized dog 102, which survived 25 days. Blood-sugar at two days after operation was 291 mgm.; at 7 days 202 mgm.; at 15 days 253 mgm.; and at 22 days 250 mgm.; the average, 250 mgm. per cent. The urine varied from 3+ to 4+ throughout. Macroscopic and microscopic studies revealed that the lungs, kidneys, liver, omentum and diaphragm were peppered with miliary and conglomerate tubercles. All these structures contained many tubercle bacilli, both intracellularly and extracellularly. Photomicrographs of tubercles in the lungs, kidneys, and liver of this animal are reproduced in figures 1 to 6. Tubercles in the dog are composed of epithelioid cells, intermingled with monocytes, lymphocytes,

Fig. 1

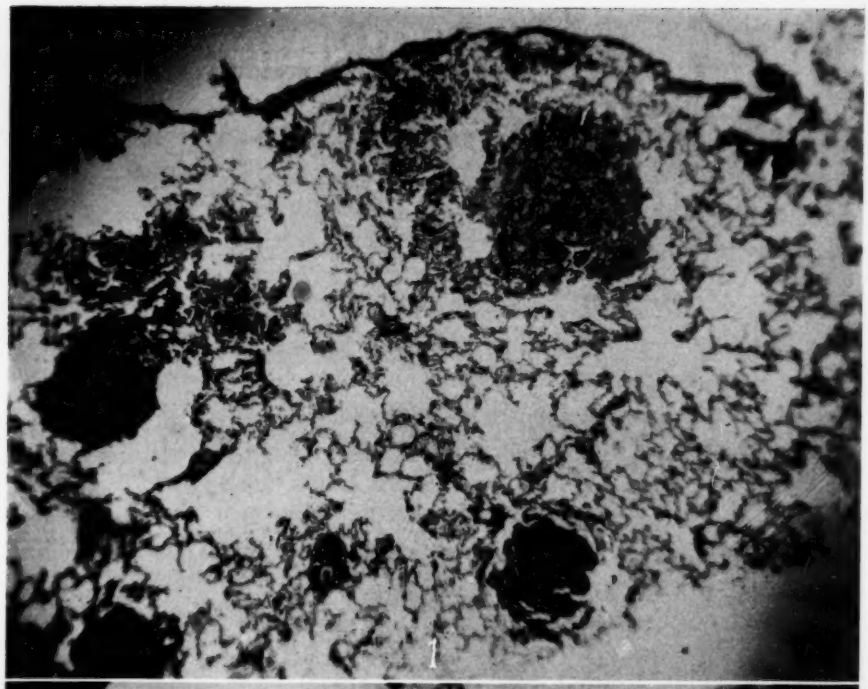
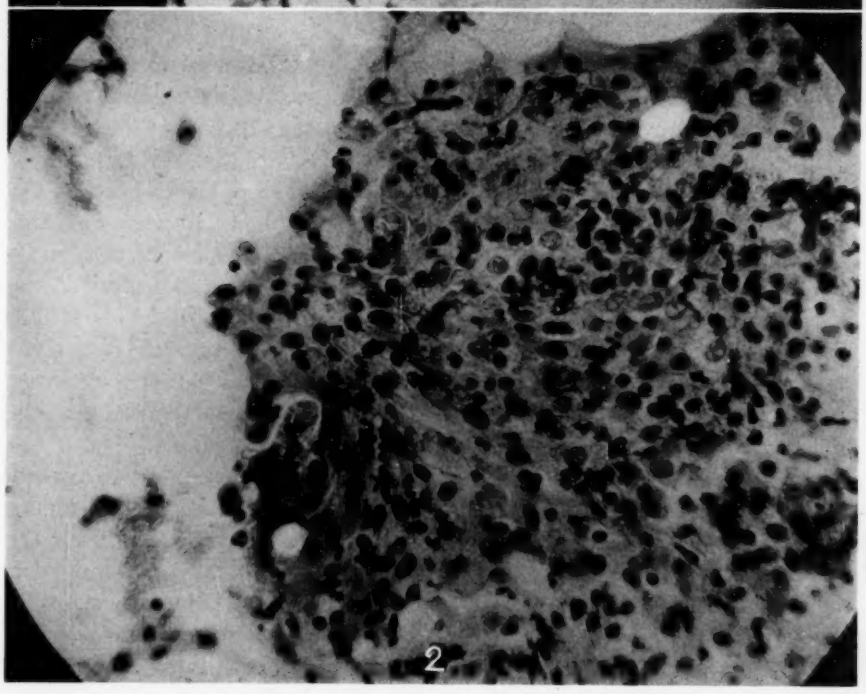


Fig. 2



PHOTOMICROGRAPHS OF DIABETIC DOG 102

Infected intravenously with bovine strain, B1, 1 mgm. per pound body-weight

Fig. 1. Lungs showing nodules which are made up of conglomerate tubercles; low power.

Fig. 2. Same section as fig. 1, under high power. The tubercle is made up of epithelioid cells, monocytes, lymphocytes and some polymorphonuclear leucocytes. Note the absence of giant cells.

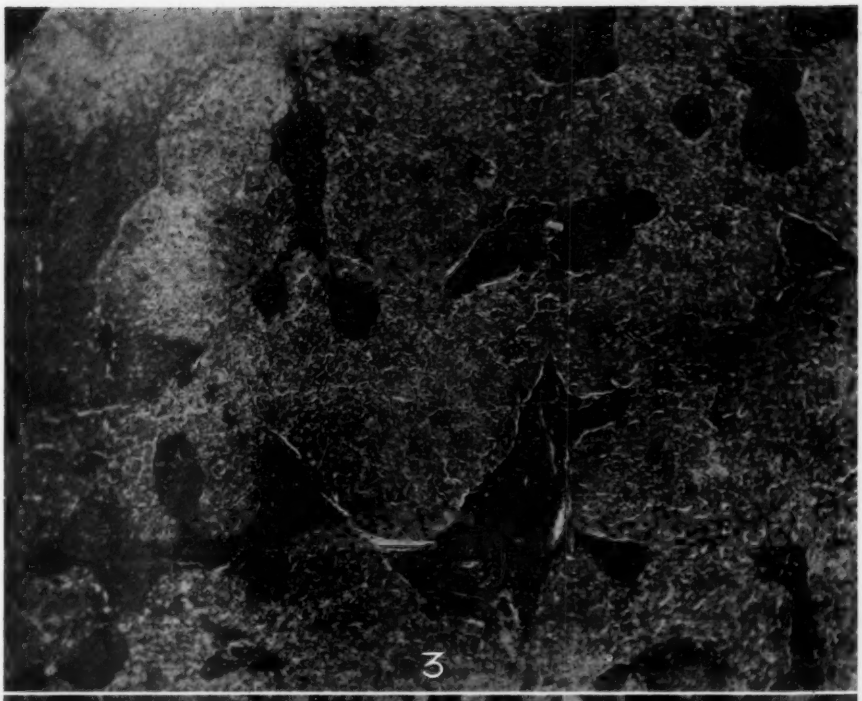


Fig. 3

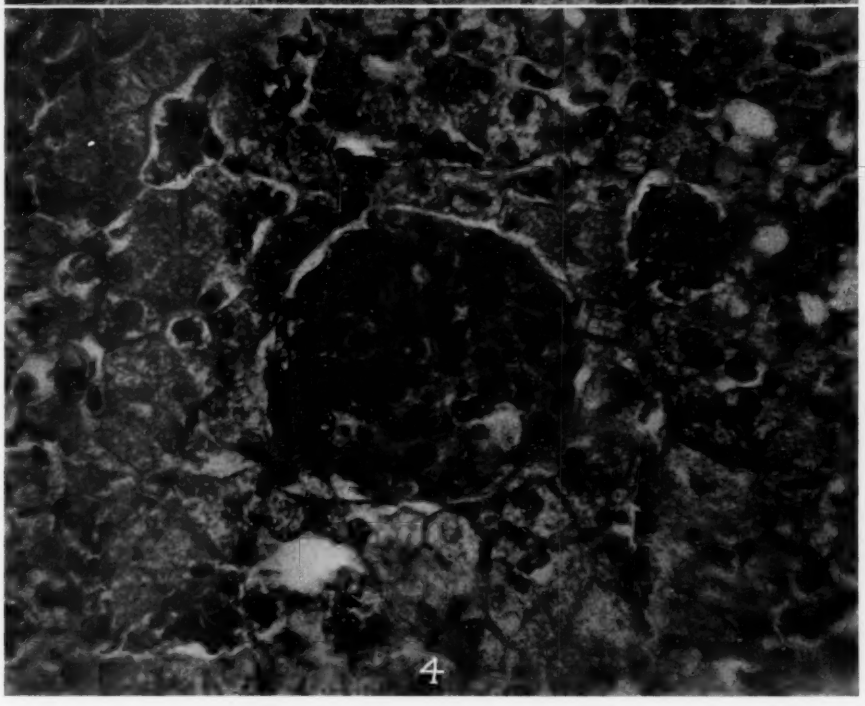


Fig. 4

Fig. 3. Conglomerate tubercles of liver; low power. Note the involvement of interlobular spaces.

Fig. 4. Single tubercle of liver, under high power, made up mostly of epithelioid cells, some lymphocytes, polymorphonuclear leucocytes, and some red cells.

Fig. 5

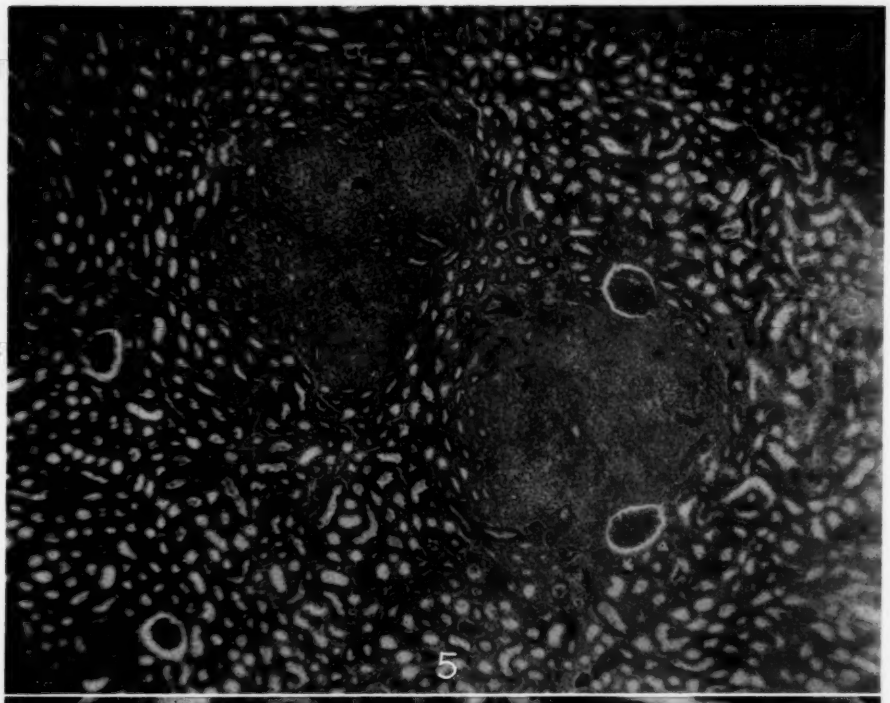


Fig. 6

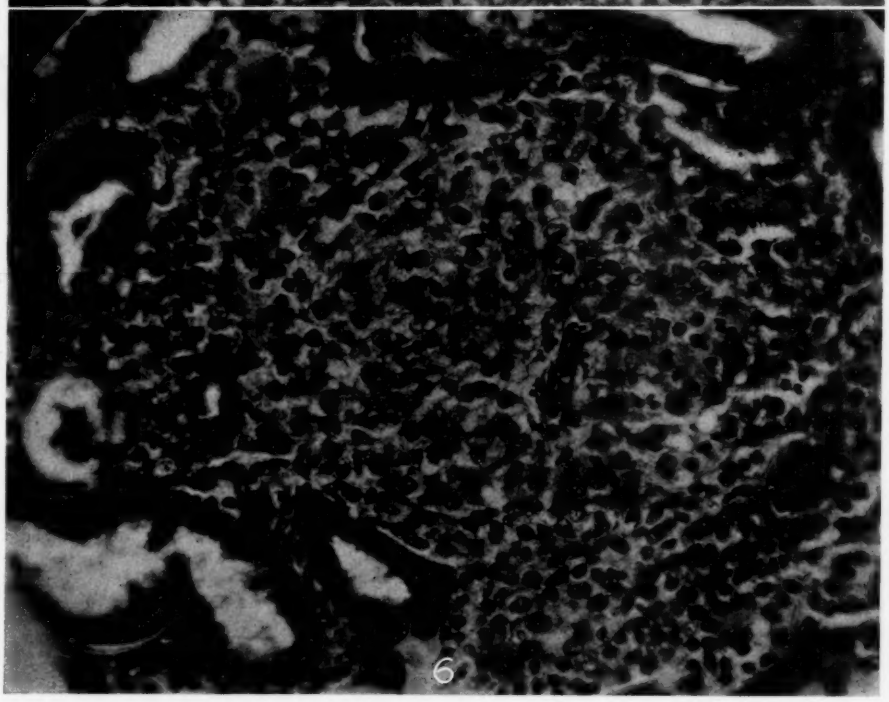


Fig. 5. Kidney showing conglomerate tubercles. Note that the periphery of these tubercles is not distinct.

Fig. 6. Kidney, under high power. Note again absence of giant cells, and the presence of polymorphonuclear leucocytic infiltration.

polymorphonuclear leucocytes, and occasionally erythrocytes. It is of interest that there were no giant cells in these tubercles; this is characteristic of tuberculosis in the dog and in all other carnivora (Fox). Control dog 101 was killed 44 days after infection, and microscopic studies showed that the liver was moderately infiltrated; all the rest of the organs were negative.

This study demonstrates that tuberculosis develops sooner, more severely, and in a more generalized form in the diabetic dog than in the control animal.

It is of course true that the nonpancreatectomized controls were not subjected to so severe a devitalization as were the pancreatectomized dogs. Pancreatectomy is a major operation, requiring one to one and one-half hours to perform, and leaving the animal in a weakened condition for several days. Moreover, the pancreatectomized animals were deprived not only of insulin secretion but of all the digestive enzymes of the pancreas (trypsin, amylopsin, steapsin). As already stated, attempts were made to compensate for the loss of digestive enzymes by the daily addition of pancreatic substance to the food; but for the first few days after operation the animals were fed only with difficulty, and during this period they lost considerable weight. Deprivation of the digestive enzymes, of course, leads to loss of weight, and therefore to a lowered resistance. However, evidence has been obtained which makes us believe that the lowered resistance to the tubercle bacillus is due mainly to faulty carbohydrate metabolism in the insulin-deprived animal. We were led to this conclusion by a study of those animals that developed only a temporary diabetes following pancreatectomy.

This study included 3 animals from our first experiment, and 2 from our second series. The three dogs (nos. 680, 607 and 684) from our first group were infected intraperitoneally with the human strain H37 in doses of 1 mgm. per pound body-weight.

One of the 3, dog no. 680, died of peritonitis 16 days after infection. The blood-sugar 24 hours after operation was 183 mgm. per cent. Five days after operation it fell to 127 mgm. per cent. The average blood-sugar for 4 determinations was 130 mgm. per cent. For the first 5 days, a trace of reducing sugar was found in the urine. We hesitate to classify this dog either as a true diabetic or as a temporary one. During the entire 16 days after operation the animal vomited and refused food, and this might easily account for the lowering of the blood-sugar. At autopsy we made an attempt to identify pancreatic tissue, but were unable to ascertain whether or not any of it had regenerated, because of the severe purulent peritonitis and degeneration of the

tissues. Microscopic examination showed a few epithelioid tubercles in the lung, liver, kidney and mesenteric lymph nodes.

Dog 607 lived 124 days after infection. It never developed a pronounced hyperglycaemia, although the blood-sugar was higher than before operation, varying from 148 mgm. per cent to 87 mgm., with an average of 117 mgm. per cent for 14 determinations. The urine was always negative for reducing sugar. In spite of the fact that this dog consumed large quantities of food, it became severely emaciated; at the time of infection it weighed 15 kg., and before death only 8.9 kg. Microscopic studies failed to reveal any tuberculosis. A small amount of pancreatic tissue was detected at the lesser curvature of the stomach.

The third dog in this group, 684, showed a blood-sugar of 161 mgm. per cent 24 hours after pancreatectomy. Four days later it was 118 mgm. per cent. No hyperglycaemia was found in subsequent determinations. The urine showed a trace of sugar on the first test, and was negative afterward. The animal weighed 12.8 kg. at the beginning of the experiment, and at death 10 kg. It was killed 316 days after infection, and autopsy studies showed no tuberculosis. Some pancreatic tissue was found along the course of the gut.

The two pancreatectomized animals (105 and 106) from the second group were infected with B1, 1 mgm. per pound body-weight, intravenously, as were the rest of the dogs in this group. Dog 106 was killed 25 days after infection. On the 2nd day after operation the blood-sugar was 182 mgm., on the 12th day 77 mgm., and at 20 days 78 mgm. per cent. The urine was negative on 4 tests. The animal's initial weight was 12.7 kg., and its final weight was 9.3 kg. Dog 105 died 32 days after infection. The blood-sugar on the 3rd day after operation was 285 mgm., on the 7th day 222 mgm., on the 11th day 84 mgm., and on the 26th day 132 mgm. per cent. The urine was 4+ on the 6th day, and all other determinations were negative. The animal weighed 18.2 kg. at the time of infection, and 12 kg. when it died. In these two pancreatectomized animals the blood-sugar soon returned to normal. Autopsy studies showed some regeneration of pancreatic tissue along the course of the gut in both of the animals, apparently enough to keep the blood-sugar at a normal level. In spite of the fact that they consumed large amounts of food, both dogs were extremely emaciated before death. Neither of these two animals showed any tuberculosis at autopsy.

Combining both series of experiments: We had one pancreatectomized dog which developed a few tubercles in various organs, but, in which, because of its peritonitis, the diabetic status was undetermined and no regeneration of pancreatic tissue could be demonstrated. Of the four other dogs with temporary hyperglycaemia, none developed tuberculosis. In contrast to these findings, nine of the ten diabetic dogs became tuber-

culous, and in certain cases the disease was demonstrated at autopsy a very short time after infection. These pancreatectomized dogs which failed to develop permanent hyperglycaemia serve as interesting controls on the effect of deprivation of the digestive enzymes of the pancreas. For, as may be seen from tables 1 and 2, this group underwent a loss of weight equal in severity to that of the diabetic dogs. The factor of inadequate nutrition in the group of pancreatectomized animals may therefore be relegated to a distinctly secondary rôle.

While one of our controls (nonpancreatectomized) showed moderate tuberculosis of the liver, and another had a few early tubercles in the kidney, their condition was in marked contrast to that of diabetic dog 102, which lived only 25 days (as compared to 44 days in the case of the controls), and showed severe involvement of many of the parenchymatous organs. A comparison of this latter animal with the pancreatectomized (but nondiabetic) dog 106, which also lived 25 days, but developed no tuberculosis, brings into sharp contrast the effect on resistance of true diabetes and temporary hyperglycaemia.

SUMMARY AND CONCLUSIONS

The dog is highly resistant to mammalian tubercle bacilli. In our first experiment we found that the human strain of tubercle bacilli, H37, did not infect the control animals, although large doses were injected intraperitoneally (1 mgm. per pound body-weight); whereas 6 of our 7 diabetic (pancreatectomized) dogs developed tuberculosis. In our second experiment we employed a pathogenic bovine strain, B1, injected intravenously, 1 mgm. per pound body-weight. Two of our 3 control dogs developed tuberculosis, one having a few tubercles in the kidney, the second showing moderate tuberculosis of the liver. In sharp contrast were the results obtained with the pancreatectomized diabetic animals: all three became tuberculous, and the disease was always more invasive, involving more organs, particularly in dog 102 which was infected only 25 days but in which most of the parenchymatous organs were extensively infiltrated with tuberculous lesions. The conclusion may therefore be drawn, that the dog, when rendered diabetic by pancreatectomy, becomes vastly more susceptible to tubercle bacilli.

Four of our 5 pancreatectomized dogs, in which the diabetes was temporary due to regeneration of pancreatic tissue, failed to develop tuberculosis, in spite of the fact that they lost weight and were extremely emaciated before death. It may therefore be concluded that the

increased susceptibility to the tubercle bacillus was not due to the lack of the pancreatic digestive enzymes and consequent emaciation, but much more likely to faulty carbohydrate metabolism which results from the absence of islet-cell secretion (insulin).

We wish to express our thanks to Drs. Louis M. Rousselot, Rudolph M. Schullinger, from the Department of Surgery, and Benjamin M. Berg, from the Department of Pathology, for their valuable aid in the technique of pancreatectomy.

BIBLIOGRAPHY

BANYAI, A. L.: Amer. Rev. Tuberc., 1931, xxiv, 650.
CRONER, W.: Deutsch. med. Wchnschr., 1903, xxix, 821.
FITZ, R.: Am. J. Med. Sc., 1930, clxxx, 192.
FOX, H.: Disease in captive wild mammals and birds, J. B. Lipincott Co., Phila., 1923, p. 499.
JOSLIN, E. P.: Treatment of diabetes mellitus, Lea & Febiger, Phila., 1928.
LONG, E. R., AND VORWALD, A. J.: Amer. Rev. Tuberc., 1930, xxii, 636.
ROOT, H. F.: New England J. Med., 1934, ccx, 1.
ROSENBERG, N., AND WOLF G.: Klin. Wchnschr., 1927, vi, 936.
STEINBACH, M. M., AND DESKOWITZ, M.: Proc. Soc. Exp. Biol. & Med., 1933, xxx, 1053.
WINDLE, B. C. A.: Dublin J. Med. Sci., 1883, lxxvi, 112.

HEPATIC FUNCTION IN PULMONARY TUBERCULOSIS

Further Studies[1]

JOHN H. STEIDL AND FRED H. HEISE

In a previous communication (1) we pointed out that the liver damage found at autopsy in so many cases of pulmonary tuberculosis can be demonstrated in a large proportion of very ill patients during life. Abnormal results were obtained in many of these cases when using several of the currently accepted tests of hepatic function. The tests used were the icterus index, the bromsulphalein, the galactose tolerance, the congo-red, and the cinchophen-oxidation test of hepatic cell-function described by Lichtman (2) (the congo-red test is a test of amyloid disease rather than of hepatic function). Of the tests used we found that the cinchophen-oxidation test gave the highest number of positive results. Further studies (3) with the cinchophen-oxidation test showed that just as great disturbances of cinchophen metabolism occurred in minimal as in advanced cases; the extent, character and activity of the disease seemed to exert little or no influence on the metabolism of cinchophen.

We wished to determine whether the abnormal oxidation of cinchophen occurring in mild cases of tuberculosis would be corroborated by the other tests of liver function which we had used in the series of far-advanced, active cases. Thirty-one ambulant cases were therefore selected: eleven because of a persistently elevated cinchophen test; the others were the 20 consecutive ambulant patients mostly recently admitted to the Trudeau Sanatorium.

In all our work we have accepted the various tests of hepatic function at their currently estimated value as found in the literature. We have no formal opinion as to the merits of any individual test, or the relative merit of the various tests.

Icterus Index

Because haemolysis is regarded as an important source of error in this test, all sera were tested for occult blood just before reading; any sera giving a positive reaction were discarded.

[1] From the Trudeau Sanatorium, Trudeau, New York.

Twenty-four of 31 patients (77 per cent) had an icterus index above 7, while the range was from 4 to 14.7.

Bromsulphalein Test

After the injection of 2 mgm. per kg. body-weight, blood was withdrawn at five and again at thirty minutes. While some authors consider even a trace of color at thirty minutes as a positive result, we have taken any reading at thirty minutes above 3 per cent as a positive result. This is merely an arbitrary choice which seems preferable to indicating small amounts of color as a "trace." Twelve of 28 patients (42 per cent) gave readings above 3 per cent at 30 minutes.

Congo-Red

As in the case of the icterus index, because of the error introduced by haemolysis, all sera were tested for occult blood before reading, and any giving a positive result were discarded. A microcolorimeter was used, and all blood was collected in the laboratory. Of 24 patients submitted to this test, 3 gave readings of 33 per cent retention of the dye and one of 54 per cent, while the remainder were normal. Thus 16 per cent gave an abnormal reading.

Galactose Test

Because of the confusion in the literature as to the exact line of demarcation between a normal and an abnormal excretion of galactose, this test was discontinued after 11 patients of this series were submitted to it. Six of the eleven (54 per cent) either excreted more than 2 gm. after the ingestion of 40 gm. of galactose, or the concentration of galactose in the urine during the first two hours was above ten parts per thousand, or both. This is accepted by some authors as the criterion of a positive test. Others would regard the excretion of more than a gram as suspicious. However, only one of our cases excreted more than 3 gm., which is accepted by many as the upper limit of normal. We feel that much of the confusion as to what constitutes an abnormal excretion is due to the efforts to use this test to differentiate obstructive from non-obstructive jaundice. Since disturbance of carbohydrate metabolism in tuberculosis has been observed by others, and since truly normal controls rarely excrete more than 2 gm., we are inclined to believe that six (54 per cent) of these patients show an inadequacy of galactose metabolism. However, these results are open to several interpretations depending on the standard which one accepts as normal.

Cinchophen-Oxidation Test

Twenty-nine of the 31 patients (93 per cent) gave a positive result to the cinchophen-oxidation test; the excretion varied from 71 to 362 mgm.

Quantitative Van den Bergh Test

Dr. Arnold Rilance, who did the Van den Bergh tests on these patients, used the technique of Thannhauser and Anderson (4). The standard consisted of 2.161 gm. of pure anhydrous cobalt sulphate in 100 cc. of distilled water. Reagent A consisted of 0.5 gm. of sodium nitrite in 100 cc. of distilled water. Reagent B consisted of 1 gm. of sulphonilic acid in 15 cc. of concentrated HCl made up to 1000 cc. of distilled water; 0.75 cc. of reagent A was mixed with 25 cc. of reagent B, and 0.5 cc. of this mixture was added to 1 cc. of serum. After standing two or three minutes 2.5 cc. of 95 per cent alcohol was added. One cubic centimetre of saturated ammonium-sulphate solution was then added. The tube was then mixed and centrifugated. The color of the alcoholic layer was then compared in a colorimeter with the standard cobalt solution which was equivalent to 0.5 mgm. of bilirubin per 100 cc. of blood.

Eleven of 20 patients had blood-serum containing more than 0.50 mgm. of bilirubin, the highest reading being 1.5 mgm.

Urobilogen Test

The concentration of urobilogen in the urine was determined according to the dilution method of Wallace and Diamond (5). If positive in a dilution of more than 1–20, the result was considered pathological. Nine of 25 patients excreted urine which gave a positive result in dilutions greater than 1–20, the highest being 1–60. Ten others excreted urine which gave a positive test in a dilution of 1–20.

Extent of Disease

From a study of table 1 it is apparent that there is no close correlation of the extent of pulmonary tuberculosis and the evidence of hepatic insufficiency.

Activity of Disease

The patients were divided into three groups according to the activity of the disease. The first and most active group consisted of those whose X-ray films appeared to show active disease, and who were considered symptomatically active, largely on the basis of elevation of pulse and

temperature. Those of the second group were considered symptomatically inactive, but the disease as shown in the X-rays appeared active. The third group were considered inactive, both from the appearance of their X-ray films and from a consideration of their symptoms.

TABLE 1

Extent of disease

	MIN.	M.A.
Average icterus-index reading	9.6	8.3
Average bromsulphalein reading	2.7	4.2
Average cinchophen excretion	222	191
Average galactose excretion	2.05	1.80
Average urobilogen reading	1–27	1–21
Average quantitative Van den Bergh	0.67	0.65
Percentage of patients with abnormal icterus index	77	62
Percentage of patients with abnormal bromsulphalein	37	50
Percentage of patients with abnormal cinchophen	89	95
Percentage of patients with abnormal urobilogen	66	25
Percentage of patients with abnormal Van den Bergh	50	53

TABLE 2

	ROENTGENOLOGICALLY ACTIVE; SYMPTOMATICALLY ACTIVE	ROENTGENOLOGICALLY ACTIVE; SYMPTOMATICALLY INACTIVE	ROENTGENOLOGICALLY INACTIVE; SYMPTOMATICALLY INACTIVE
Average icterus-index reading	10.7	8.5	7.9
Average bromsulphalein reading	3.5	5.6	3.0
Average cinchophen excretion	170	191	208
Average galactose excretion	1.89	1.76	2.0
Average urobilogen reading	1–33	1–21	1–22
Average quantitative Van den Bergh	1.11	0.83	0.50
Percentage patients abnormal icterus index	66	87	74
Percentage patients abnormal bromsulphalein	50	50	38
Percentage patients abnormal cinchophen	100	100	90
Percentage patients abnormal urobilogen	33	37	35
Percentage patients abnormal Van den Bergh	100	100	33

There were 3 patients in the first group, 9 in the second, and 19 in the third.

From a study of table 2 it is apparent that there is no rigid correlation between the evidence of hepatic insufficiency and the activity of pulmonary tuberculosis. It is in general true, however, that the average readings for the icterus index, the urobilogen test, and the quantitative Van den Bergh test are highest in the patients with more active disease,

and that the percentage of patients showing an abnormal Van den Bergh test is highest in the groups with active disease. Whether or not this will hold true in a larger series of cases remains to be seen.

Comment

Including the cases reported here, we have studied more than 50 tuberculous patients with a wide variety of liver-function tests, and more than 200 patients with the cinchophen-oxidation test alone. We have been surprised to find the evidence of hepatic insufficiency quite as marked in the present group of rather mild cases as in a previously reported group of very ill patients.

Considering the numerous functions of the liver and the burdens placed upon it in times of stress, it is not surprising that this organ should suffer during a prolonged chronic infection such as tuberculosis. From autopsy material we have the evidence of fatty, amyloid and fibrous changes, and the existence of tuberculous foci in the liver. It is also possible that such an organ may suffer from physiological insufficiency without concomitant structural damage. Considering the large factor of reserve in the liver, it is somewhat surprising that such insufficiency can be demonstrated during life with the usual tests of liver function, since these tests are often positive only in the presence of rather gross variations from the normal. Such, however, appears to be the case. To support the validity of these results, it has also been pointed out that, when a diabetic patient develops tuberculosis, the level of blood-cholesterol (with the metabolism of which the liver is largely concerned) falls, and does not rise under the provocations which elevate the blood cholesterol in uncomplicated diabetes.

Having shown that hepatic insufficiency so commonly occurs, and can be demonstrated during life by the commonly accepted tests of liver function, it becomes a more difficult problem to explain how this insufficiency occurs. It is apparently unrelated to the extent or activity of the pulmonary tuberculosis, except that there is a rather loose general correlation of the bile-pigment metabolism and the activity of the pulmonary tuberculosis. Even this correlation fails us when considering the percentage of patients with various degrees of activity showing abnormal icterus indices and urobilogen tests. The sedimentation rate shows no correlation, nor does the duration of the tuberculosis, as judged by the patients symptoms. However, there appears to be no satisfactory method of determining the duration of the tuberculosis in any given patient.

TABLE 3

Comparative liver-function tests

ICTERUS INDEX	CINCHOPHEN	BROMSULPHALEIN	CONGO-RED RETENTION	GALACTOSE		VAN DEN BERGH	UROBILOGEN	SEDIMENTATION	ACTIVITY		EXTENT OF DISEASE	CHARACTER OF DISEASE
				1st specimen	Total weight				R	S		
	mgm.		*per cent*	*parts per M.*	*gm.*							
4	144	5m.—35%; 30m.— 0	25			Normal	Less than 1–10	2	0	0	Min.	P
4.5	161	5m.—15%; 30m.— 0	29	15	2.82		1–20	2	+	+	M.A., cavity	P
4.76	166	5m.—40%; 30m.— 5%	27	8	1.71		1–20	10	+	0	M.A.	P
6	80	5m.—20%; 30m.— 3%				Normal	1–20	4½	0	0	Min.	P
6	135	5m.—30%; 30m.— 5%				0.98	1–20	1	0	0	M.A.	P
6	221	5m.—10%; 30m.— 0	23			Normal	1–10	16	0	0	M.A., pntx.	P
6.39	71	5m.—30%; 30m.— 0	25			Normal	1–20	2	0	0	M.A.	P
7.2	153					Normal	1–20	6½	0	0	M.A.	P
7.28	138	5m.—35%; 30m.— 2%	33.3			0.51	1–30	24½	+	0	M.A.	P
7.4	259	5m.—25%; 30m.—no trace	33	12	3.04			15½	+	0	M.A	P
7.6	230	5m.—22%; 30m.—trace	14.8	7	2.40			3	0	0	Min.	P
7.6	181						1–10	13½	+	0	M.A., cavity, pntx.	E
7.72	243	5m.—65%; 30m.—20%	33	12	1.77	1.2	1–30	1	+	0	M.A., cavity, pntx.	E
7.73	177	5m.—20%; 30m.— 2%	19			Normal	1–10	13½	0	0	M.A.	P
7.9	170	5m.—27%; 30m.—trace	13	15	1.80	0.54	1–20	23	+	0	F.A., cavity	P
8	176	5m.—35%; 30m.— 0						3	0	0	M.A.	P
8	214	5m.—20%; 30m.— 5%	7						0	0	M.A.	P
8	153	5m.—25%; 30m.— 3%	0					6½	0	0	M.A.	P
8.11	362	5m.—35%; 30m.— 2%	10			Normal	1–20	14	0	0	M.A.	P
8.36	284	5m.—30%; 30m.— 4%	17			1.29	1–30	3½	0	0	Min.	P
8.7	158	5m.—100%; 30m.—10%	54	4	1.43	1.10	1–10	5	+	0	M.A., cavity	P
9	184	5m.—25%; 30m.— 0	0			0.88	1–40	11	0	0	Min.	P
10	271	5m.—35%; 30m.— 5%	0			Normal	1–40	6½	0	0	M.A.	P
11	227	5m.—35%; 30m.— 5%	24					6	0	0	M.A., pntx.	P
12.5	208	5m.—35%; 30m.— 3%				1.0	1–40	18	+	0	Min.	P
12.5	322	5m.—25%; 30m.— 8%	0	9.9	1.5		1–30	2	0	0	Min.	P
12.85	198	5m.—55%; 30m.— 5%	6	0.3	0.8	0.65	1–10	1	+	0	M.A., cavity	P
13	164					1.5	1–60	½	+	+	M.A., cavity	P
13	242	5m.—25%; 30m.— 0	16			Normal	1–20	3	0	0	Min	P
14	307	5m.—40%; 30m.— 7%	10	14	2.30		1–30	3	0	0	Min.	P
14.7	186	5m.—15%; 30m.— 7%	0	7	0.97	0.73	1–20	3	+	+	M.A., cavity, pntx.	E

E—Exudative. P—Productive. Pntx.—Pneumothorax. R—Roentgenological. S—Symptomatic. Min.—Minimal. M.A.—Moderately advanced. F.A.—Far advanced.

It is possible that the liver is damaged during the dissemination of tubercle bacilli through the blood-stream, as in Ranke's second stage. Not much is known about such dissemination, however, and any discussion of this possibility must of necessity remain highly theoretical.

The possibility that hepatic insufficiency may be a result of hepatic allergy must be considered. In a group of 70 patients it was found that, in general, those whose skins were most sensitive to Old Tuberculin excreted the greatest amount of oxycinchophen when subjected to the cinchophen-oxidation test. However, we are unaware of any proof that hepatic allergy parallels cutaneous allergy.

CONCLUSIONS

Hepatic insufficiency, as demonstrated by the currently accepted tests of liver function, occurs quite commonly in patients afflicted with pulmonary tuberculosis. In the present group of 31 ambulant patients with a slight or moderate amount of pulmonary tuberculosis, there appeared to be quite as much evidence of hepatic insufficiency as was found in a group, previously reported by us, of very ill patients with advanced disease.

REFERENCES

(1) STEIDL, J. H., AND HEISE, F. H.: Studies of liver function in advanced pulmonary tuberculosis, Am. J. M. Sc., 1933, clxxxvi, 631.

(2) LICHTMAN, S. S.: Arch. Int. Med., 1931, xlviii, 98.

(3) STEIDL, J. H., AND HEISE, F. H.: The cinchophen oxidation test of liver function in pulmonary tuberculosis, Am. J. M. Sc., 1934, clxxxviii, 81.

(4) ELTON, N. W.: J. Lab. & Clin. Med., 1931, xvii, 1.

(5) WALLACE, G. B., AND DIAMOND, J. S.: The significance of urobilogen in the urine as a test for liver function, Arch. Int. Med., 1925, xxxv, 698.

THE CINCHOPHEN-OXIDATION TEST OF HEPATIC FUNCTION IN PULMONARY TUBERCULOSIS

A Study of Its Variation[1]

JOHN H. STEIDL AND FRED H. HEISE

In previous publications (1) (2), it has been demonstrated that hepatic insufficiency occurs in quite a high percentage of all types of chronic pulmonary tuberculosis. Of the various tests of liver function used in previous work, the cinchophen-oxidation test of Lichtman (3) has been found most frequently positive and, therefore, possibly the most sensitive. In order to determine the course of hepatic insufficiency over a period of time in pulmonary tuberculosis, the cinchophen-oxidation test was therefore selected, although it is a new test, the exact value of which has not been corroborated.

The test was done on admission and repeated every six weeks in a group of 109 consecutive unselected patients admitted to the Trudeau Sanatorium. The time over which a patient was observed by this test varied from six months to one year. The test was positive on admission, that is, excretion of more than 100 mgm. in 102 of the 109 patients (94 per cent). The excretion became normal in nine of the 102 patients and all but one of the nine remained normal during residence.

In 56 patients the excretion of oxycinchophen was materially less at discharge as compared to admission. Of these, 55 remained well and one relapsed. The excretion in 21 patients remained stationary (that is, did not vary more than 20 mgm.). Of these, 17 remained well and four relapsed. In 25 patients the excretion was materially more at discharge than at admission. Of these, 20 remained well and five relapsed.

Since chest X-ray examinations were made and blood sedimentation rates were done every six weeks simultaneously with the cinchophen-oxidation test, it was possible at short intervals to follow the variation in these three factors. In 45 per cent of the cases all three tests grew better or worse simultaneously. In 16 per cent of the cases the cinchophen-oxidation test agreed with the changes seen in the X-ray films, in 21 per cent with the change in the sedimentation rate, and in 18 per cent it

[1] From the Trudeau Sanatorium, Trudeau, New York.

stood alone. The general trend of the cinchophen oxidation in 70 per cent of cases was the same as the sedimentation rate, and different in 30 per cent. In 75 per cent of cases the general trend of the cinchophen-oxidation test coincided with improvement or increase as seen in the X-ray films. In 25 per cent there was divergence.

Extension of disease appearing in the X-ray films on 23 occasions was preceded by oxycinchophen excretion varying from 90 to 420 mgm., the average being 235 mgm. On 10 of these occasions the extension was preceded by an excretion of less than 200 mgm. and on 13 occasions by an excretion of more than 200 mgm.

We have noted no ill effects from the administration of 450 mgm. of cinchophen every six weeks.

COMMENT

Hepatic insufficiency, as judged by the cinchophen-oxidation test, persisted in 92 per cent of a group of 102 patients under observation from six months to one year. Approximately one-half of these patients showed material improvement in, but not complete restoration of, hepatic function during the period of observation. Most of the relapses or extensions of pulmonary tuberculosis occurred in patients whose hepatic function failed to improve.

REFERENCES

(1) STEIDL, J. H., AND HEISE, F. H.: Studies of liver function in advanced pulmonary tuberculosis, Am. J. Med. Sc., 1933, clxxxvi, 631.

(2) O'CONNOR, J. B., YOUNG, H., STEIDL, J. H., AND HEISE, F. H.: The cinchophen oxidation test of liver function in pulmonary tuberculosis, Ibid., 1934, clxxxviii, 81.

(3) LICHTMAN, S. S.: Arch. Int. Med., 1931, xlviii, 98.

RESULTS OF ABDOMINAL COMPRESSION IN PULMONARY TUBERCULOSIS[1,2]

BURGESS GORDON

Symptomatic improvement in emphysema (1) (2) (3), bronchiectasis, chronic bronchitis and pulmonary tuberculosis (3) has been obtained from the use of special abdominal supports. Striking effects are (1) lessened dyspnoea in emphysema, as especially noted by Alexander and Kountz (1), and Meakens and Christie (2); and (2) decrease of racking cough, fatigue and discomfort in the abdomen with greater ease of expectoration, as observed in the pulmonary infections at the Jefferson Hospital (3). Various explanations have been suggested, the most significant of which concerns the mechanism of expiration and intra-abdominal pressure.

It appears that expiration is a passive act, due largely to the elastic recoil of the lungs. This contraction exerts a constant "pull" on the thoracic wall and gives rise to a negative intrapleural pressure. With loss of elasticity there is a diminution of pressure and the lungs remain inflated unless the expiratory act becomes positive. It is possible, under certain circumstances, for the pressure itself to become positive, especially with separation of the pleura and vigorous action of the expiratory muscles of the thorax. Thus a compensatory factor is developed which compresses the lungs and increases their activity. However, with an excessive rise of pressure or marked distention of the lungs there is a displacement of the diaphragm. Thus, the mechanism may defeat itself, since the diaphragm is essentially a muscle of inspiration with no special power of its own to resist high intrathoracic pressures.

It is known that displacement of the diaphragm can be prevented by contracting the muscles of the abdomen. This increases the intra-abdominal pressure which in turn supports the diaphragm and favors expiration. Unfortunately, in chronic pulmonary disease the abdominal

[1] From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest of the Jefferson Hospital, Philadelphia, and the White Haven Sanatorium, White Haven, Pennsylvania.

[2] Read before the Section of General Medicine, College of Physicians, Philadelphia, Pennsylvania, February 25, 1935.

muscles are often so relaxed and weakened as to render the mechanism practically useless. Furthermore, in this state, sudden and often tetanic-like movements of the diaphragm may occur. Evidently the supporting influence as well as the shock-absorbing effect of the diaphragm is lost. For this reason, the application of a binder to hold and compress the abdomen seems logical. Experience shows that with the diaphragm thus restored to a normal expiratory position and controlled during violent coughing, there is a mechanism of definite value for the relief of symptoms.

Other phenomena are no less important and interesting. A striking example is the adaptability of the bronchi and alveoli to changes in the volume of the lungs, often suddenly, as in cough. In the normal lung, the adjustments are purely physiological, but one might wonder about the effects in disease. For example, dyspnoea is influenced by the accumulation of pulmonary secretions, resulting in an actual decrease in the air space of the lungs. Although cough may be essential for drainage, its value is offset by trauma to the lungs, fatigue, digestive disturbances and abdominal hernia. Willauer (4) has observed in thoracoscopic studies that a remarkable expansion of emphysematous blebs of the lung occurs during forceful expirations. Likewise, when air is expelled forcefully from the lungs, with the glottis closed, as in coughing and straining, the compressed air distends the alveoli, bronchi and pulmonary cavities. It is recognized also that, with bronchial strictures of the "ball-valve" type, there is a tendency for air to be trapped in the adjacent parts of the lung and for expansion, especially of thin-walled cavities, to occur. Visualize the endless repetition of these phenomena in chronic pulmonary disease, and the possibilities of trauma will be appreciated. It is difficult to understand how a diseased lung can tolerate such changes indefinitely, especially in regions unprotected by bone and muscle, as in the apices and mediastinum.

The view that a relationship exists between certain structural characteristics of the body and the activity of pulmonary tuberculosis has been considered from the earliest times. For example, the long type of chest and the scaphoid abdomen have been associated with the unfavorable cases of pulmonary tuberculosis, whereas the rounded or athletic type of chest and the obese, full or well-developed abdomen have suggested greater resistance to the disease. The tendency of large abdominal tumors to hold pulmonary tuberculosis in abeyance has also been recognized. Two cases are described: (1) a tuberculous woman with

ascites and amyloid disease of the liver, and (2) a pregnant woman with pulmonary tuberculosis (5). Before the onset of these complications, there had been a progressive form of tuberculosis, but, with gradual increase in the size of the abdomen, a striking retrogression of the disease occurred. Similar improvement was also noted in certain patients who gained rapidly in abdominal weight. It was suggested that elevation of the diaphragm and the supporting influence of increased intraäbdominal pressure were factors in the improvement of these cases. Accordingly, a special abdominal support was developed in order to utilize the mechanism of diaphragmatic elevation in the treatment of pulmonary tuberculosis.

The present report concerns the changes in the lungs of 129 patients with essentially a bilateral, fibroid type of tuberculosis, who wore special abdominal supports from 3 to 18 months.[3] The patients had been treated in their homes or in sanatoria for at least six months, without improvement; 41 were ambulatory, 11 working because of necessity. Treatment of the lungs by collapse therapy either was not indicated or had been unsuccessful. The supports were worn day and night, except in extreme malnutrition when they were removed for short periods. Compression was discontinued, in certain cases, for three to five weeks to determine if retrogression or progression occurred independently of treatment.

Symptomatic relief from dyspnoea and difficult expectoration was the rule. Attacks of paroxysmal tachycardia were controlled in two patients; gastrointestinal symptoms improved in 9 instances; 76 gained in strength and generally "felt better." The X-rays showed improvement in the pulmonary lesions of 39 patients (12 ambulatory, 27 at rest in bed), as evidenced by a decrease in the size of cavities or their disappearance, and retrogression of the associated lesions. The largest cavity before treatment was 4.5 cm. in diameter. Eleven were located in the upper third of the lung; two in the middle third; and three in the lower third. They closed as follows: 1 in 7 weeks; 4 in 2 months; 2 in 3 months; and the remainder between 3 and 5 months. The supports were removed in 3 patients; an increase of cough followed and in about 4 weeks the cavities returned to their former size. The supports were reapplied,

[3] The supports consist of an elastic or nonelastic binder, buckles for adjusting, a central pad, one or two cross-springs for maintaining constant compression over the central part of the abdomen and hernial pads if indicated. The so-called two-spring model is most effective in patients confined to bed. They were manufactured by The Geo. P. Pilling & Son Co., 23rd and Arch Streets, and the Nulty-Coggins Co., 24 S. 16th Street, Philadelphia.

and the cavities diminished in about 5 weeks. It was interesting that 2 apical cavities, which developed during the course of artificial-pneumo-

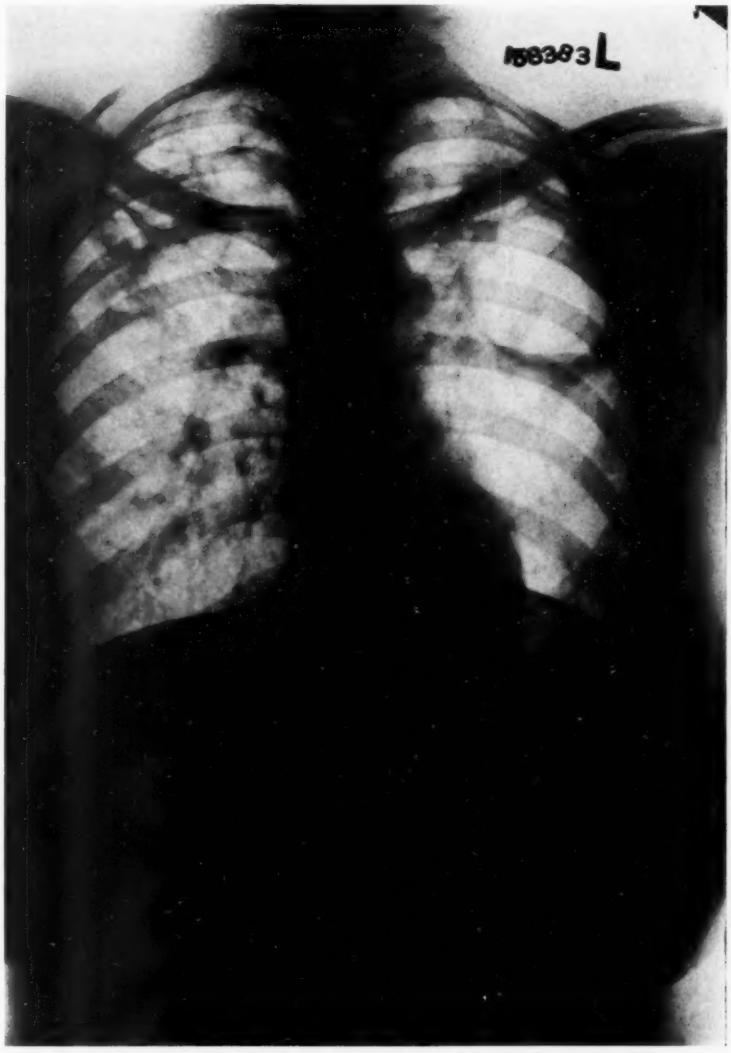


FIG. 1. Roentgenogram of tuberculosis patient (J. K.), taken by Dr. Manges-Smith, December 5, 1933. A cavity with a fluid level, 4.5 cm. in diameter, is present in the left lung.

thorax treatments, closed after the lung reëxpanded and following abdominal compression. Twelve other patients showed at first a

decrease in the size of their cavities, then more or less stationary dimensions; 8 improved sufficiently for artificial pneumothorax to be employed

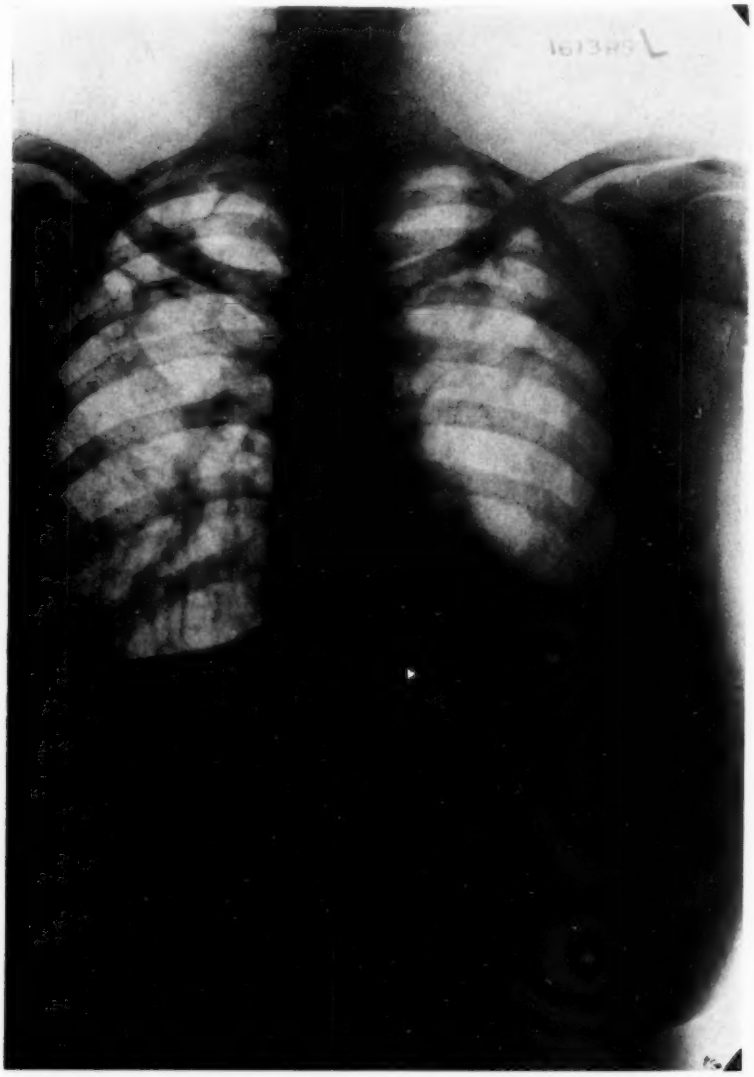


FIG. 2. Roentgenogram of the same patient (J. K.) taken by Dr. John T. Farrell, Jr., March 3, 1934, after a special abdominal support had been worn continuously for these months. The cavity has disappeared.

safely and effectively. Twenty-six patients who showed no structural improvement in the lungs (17 with thick cavity walls, 10 with marked

fibrosis) were able to exercise without untoward effects: they seemed to carry their lesions safely. The vital-capacity studies in 31 patients showed at first a reduction of 10 to 15 per cent, which indicated a decrease of the air space of the lungs; with an increase of thoracic excursions there was a gradual return to the previous figure; 19 showed no appreciable change. The greatest symptomatic relief and improvement in the lungs occurred in the patients with the well-developed abdomen and abdominal type of breathing. The unsatisfactory results, such as elevation of the temperature with increased cough and dyspnoea, were noted in those with acute extensions or with soft caseating lesions, and marked fibrosis. Six patients were unable to wear the supports because of gastrointestinal manifestations or of malnutrition.

The present study suggests that the lesions of chronic pulmonary tuberculosis are aggravated by deep vertical excursions of the lungs, difficult expectoration, and the traumatizing action of cough. It appears that elevation of the diaphragm and the supporting influence of increased abdominal pressure control the respirations, equalize the movements of the lungs in different planes, and facilitate drainage from dependent parts. The mechanism resembles bilateral phrenicectomy, with the advantage, however, that the propelling force of the diaphragm is preserved, which is of distinct value in expectoration. The diminution in the size of, or rapid disappearance of certain cavities suggests that these "cavities" were dilated sacs, expanded by increased pressure from within and stretched outwardly by the deep excursions of the lungs. It is possible that the reduced volume of air in the lungs and the controlled respirations are factors that tend to minimize their dilatation. This view is supported by the observation that cavities which had closed during abdominal compression subsequently became dilated after the binders were removed.

Another interesting feature is the development of cavities in the lungs collapsed by artificial pneumothorax and their subsequent improvement after the lung reëxpanded and following abdominal compression. The explanation for this is suggested in Korol's (6) interesting consideration of *Pascal's Law*.[4] He observed that the collapsed lung, functioning without residual air, shows greater respiratory excursions than the overlying chest-wall. Cutler (7) also observed that the lung collapsed with artificial pneumothorax may show rather large excursions. This suggests

[4] Any pressure exerted on the surface of a fluid is transmitted throughout the fluid equally in all directions. Pressure applied to any point on the surface of a fluid is exerted at all points of the container of the fluid. Both liquids and gases obey this law.

that the expanded lung under peculiar circumstances may receive greater rest than in the moderately collapsed state. The development of cavities in patients treated with artificial pneumothorax emphasises the possibility of this hypothesis. It seems not unlikely that slight limitation of the vertical excursions, combined with the usual compressing effects of the thorax, is more advisable for certain pulmonary lesions than actual collapse of the lung itself. This would be especially true in constant and violent coughing. Cooper (8) recommends abdominal compression to increase the elevation of the diaphragm in phrenicectomy. According to Christian (9), it may be useful in "testing" diaphragmatic elevation preliminary to proposed phrenicectomy. It will prevent depression of the diaphragm in pneumothorax and may improve the posture and respirations in thoracoplasty cases. While abdominal compression is not intended as a substitute for rest, diet and the recognized forms of collapse treatment, it seems reasonable to suggest its use for the chronic forms of pulmonary tuberculosis, especially in bilateral involvement, and if cough, expectoration and dyspnoea are disturbing manifestations.

CONCLUSIONS

1. Certain unfavorable results in the standard treatment of pulmonary tuberculosis are due to the traumatizing action of cough and the deep, inefficient and uncontrolled excursions of the diaphragm.

2. The findings in the present study indicate that abdominal compression, as a means for elevating and controlling the movements of the diaphragm, favors expectoration and is of value in the prevention of trauma to the lungs.

3. The roentgenographic studies show the closure of certain cavities and the retrogression of lesions.

4. Abdominal compression is suggested as a supplementary measure in the treatment of pulmonary tuberculosis.

REFERENCES

(1) ALEXANDER, H. L., AND KOUNTZ, W. B.: Symptomatic relief of advanced emphysema, Am. J. M. Sc., 1934, clxxxix, 660.

(2) MEAKINS, S., AND CHRISTIE, R. V.: Treatment of emphysema, J. Am. Med. Ass., 1934, cxciii, 384.

(3) GORDON, B.: The mechanism and use of abdominal supports and the treatment of pulmonary tuberculosis, Am. J. M. Sc., 1934, clxxxvii, 692.

(4) WILLAUER, G.: Personal communication, February 16, 1935.
(5) GORDON, B.: Abdominal conditions influencing the lung and pleural pressure in pulmonary tuberculosis, Amer. Rev. Tuberc., 1934, xxx, 72.
(6) KOROL, E.: Operation of Pascal's principle, Ibid., 1935, xxxi, 299.
(7) CUTLER, J. W.: An improved technique for selective pneumothorax, Ibid., 1930, xxii, 292.
(8) COOPER, D.: Personal communication, February 4, 1935.
(9) CHRISTIAN, H. A.: Personal communication, April 12, 1934.

A STUDY OF THE EXCRETION OF SILICON IN THE URINE OF TUBERCULOUS PATIENTS[1,2]

With a Discussion of the Rôle of Silicon in Tuberculosis

HENRY LEE

Preparations containing silicon have been used for centuries in the treatment of the many manifestations of tuberculous infections. The folk remedies for tuberculosis were herbs whose ash is extremely rich in silicon dioxide.[3] Recent years have witnessed a revival in this mode of therapy and many attempts have been made to establish a rational basis for its use. The evidence is not conclusive, but it is suggestive of possibilities for therapeutic use and also for a more thorough understanding of the healing process in tuberculosis.

The imprisonment of silicon is said to be responsible for the relatively large amount of this element found on examination of tuberculous lymph nodes. The analysis of Kahle revealed the silicon-dioxide content of a normal lymph node to be 0.14 gm. per kg. of the dried substance, while that of the calcareous lymph node of a child and of an ox were found to be 1.6 and 1.54 gm. per kg. respectively. Zickgraf found the ash of calcified bronchial lymph nodes to contain from 5 to 12 per cent silica. However, Maver and Wells reported no silica in a calcified mesenteric lymph node and believed silicon played no rôle in the healing of tuberculosis. Gerhartz and Stiegel did not always find silica in calcified bronchial lymph nodes. Kraut has found the average silicon-dioxide content of the ash of normal blood to be 1.75 per cent while the average was 1.99 in 55 tuberculous patients.

Kramer believes the tubercle bacillus similar to many plants in its tendency to extract silicon from its environment. The studies of de Schweinitz and Dorset showed the ash of tubercle bacilli to contain 0.57 per cent silica. Kramer draws an interesting analogy between the

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[2] A reprint in part of a dissertation submitted to the Graduate School of the University of Cincinnati in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Surgery, June, 1935.

[3] See appended Bibliography: Editorial, *Journal of American Medical Association*, etc.

changes which can be produced by chemical means in an oil emulsion of silicic acid and the processes which accompany the growth of the tubercle bacillus in the body. A permanent oil emulsion is formed by the addition of a minute quantity of sodium silicate to olive oil. This is said to represent fatty degeneration. The addition of lime-water will cause this emulsion to "caseate," and the bubbling of carbon dioxide through this caseous mass will induce a further change. According to Kramer, fatty degeneration represents the effect of large quantities of free silicic acid, liberated by the growth of the tubercle bacilli, on the surrounding tissues. Caseation results from the deposition of lime in this focus, and calcification follows the breakdown of the calcium silicate to form calcium carbonate, under the influence of carbon dioxide.

Schulz reports the connective tissues to be extremely rich in silica, while McNally describes the lungs of tuberculous subjects as containing somewhat more silicon dioxide than those of normal persons. Kahle ascribes the exacerbation of pulmonary tuberculosis in pregnancy to the demands made by the foetus for a bountiful supply of silicon. This would extract silicon from the tissues, and thus lead to a weakening of the wall of fibrous tissue which serves to keep the tuberculous focus in check. Robin thinks silica is withdrawn principally from the bones in pulmonary tuberculosis.

The influence of silicon on the growth of the tubercle bacillus in the body is obscured by conflicting reports. Kettle found a greater growth of tubercle bacilli in abscesses produced by the injection of silica sol than in those caused by the injection of turpentine or calcium chloride. Moreover, he found that a much greater growth of the organisms was found at the site of the injection if a suspension of silicon dioxide were injected subcutaneously and subsequently tubercle bacilli were injected intravenously. Cummins and Weatherall observed a greater local reaction following the experimental inoculation of silica sol and tubercle bacilli, without, however, an earlier or a more general dissemination. They did not find that the addition of silica sol to human blood influenced the growth of the tubercle bacillus in this medium outside the body. Price has reported that the addition of a minute quantity of sodium silicate to a modified Dorset's egg medium will stimulate the growth of the tubercle bacillus. Gardner showed that the inhalation of quartz dust would cause a reactivation of experimental pulmonary tuberculosis in guinea pigs. Kahle fed guinea pigs affected by tuberculosis an organic silicon preparation, and these animals showed a much greater connective-tissue proliferation than did the controls.

The evidence leads one to believe that the apparent beneficial influence which silicon may exert in some instances on a tuberculous infection results from the stimulation of connective-tissue proliferation, and not from any effect on the tubercle bacillus itself. Kessler observed an enormous connective-tissue proliferation in a suicide suffering from pulmonary tuberculosis, who had been treated by the oral administration of large quantities of a preparation containing silicon. Roth also reports autopsy findings to support the above view. Kobert believes the ingestion of silicates induces a hyperaemia in the involved area and also promotes the formation of connective tissue.

The many clinical reports on the use of silicon in tuberculosis are for the most part enthusiastic. Kühn observed favorable results, using an infusion prepared from the herbs, *galeopsis*, *equisetum* and *polygonum*. The silicates contained in these are in the form of alkaline silicates. Junker reported untoward complications arising from the alkaloid content of these infusions and from the alkalies liberated in the gastrointestinal tract. Bauer recommended a concentrated infusion of equisetum and believed it promoted the formation of fibrous connective tissue. Ladendorff gave tuberculous patients mineral water containing large quantities of silica and noted clinical improvement.

Because of the great variations in the amount of silicon contained in the herbs and also the uncertainty of its resorption from the gastrointestinal tract, attempts have been made to substitute other more suitable preparations. Sodium silicate has been used extensively by homeopathic physicians in the treatment of tuberculosis (Zimmer). Various organic preparations said to contain silica in its active form as silicic acid have been used. Helwig employed *silternum*, and was struck by the manner in which it brought the disease to a standstill even in cases with bacilli in the sputum and cavities already in existence. Klare and Budde, and Zeller have reported excellent results in the more proliferating forms of pulmonary tuberculosis in children after the use of *silistren*, the orthotetraglycolic ester of silicic acid. Junker recommends the oral administration of a preparation, "silcasin," consisting of 96 per cent casein and 4 per cent sodium-metasilicate. Zimmer advises intravenous and intramuscular injections of suitable preparations containing silicon and has also seen good results following oral administration. Forster also recommends several proprietary drugs containing silicon in the treatment of pulmonary tuberculosis. Scheffler, Sartory and Pellissier gave repeated courses of intravenous injections of sodium silicate (2 cc. of a 0.5 per cent

solution) for ten injections every day for the same disease. Stein observed clinical improvement and a striking deposition of calcium in the hilum lymph nodes of children after the oral administration of a proprietary drug containing iron, calcium and silicon. Helbach used *silcasin* in the treatment of 15 children with active pulmonary tuberculosis, and noted excellent results. Rosenstingl and Salomon recommended a proprietary preparation containing silicon in pulmonary tuberculosis on the basis of their clinical experience. Freund obtained remarkable clinical results with *silistren*.

Thoma reported definite exacerbations of pulmonary tuberculosis in patients treated by intravenous injections of a solution of colloidal silicic acid, *siliquid*, containing 0.3 per cent silicon dioxide. Frank treated 71 cases of tuberculosis in children involving different regions of the body with "teas" and others with *silistren*, but could observe no improvement. He was unable to note any favorable effect on experimental tuberculosis of guinea pigs treated with a silicon preparation.

The relation of silicosis to tuberculosis has been the subject of numerous reports. The incidence of tuberculosis in association with silicosis is often given as 20 to 30 per cent. Hayhurst, *et al.*, examined 912 workers in a sandstone quarry and found evidence of silicosis in 28.5 per cent and tuberculosis in 1.9 per cent. Five per cent of those with silicosis had an associated pulmonary tuberculosis. Moore reported a higher incidence of tuberculosis among workers exposed to silica dust than in coal-miners, and Hoffman, as well as many others, has found the death-rate from phthisis to be uniformly low in coal-miners. Hackmann analyzed the lungs of 37 miners for their silica content and could find no relation between the quantity present and an accompanying tuberculous infection. Greenburg determined a close correlation between the mortality rate from tuberculosis and the quantity of silica inhaled by industrial workers. Selkirk found the incidence of tuberculosis among lime workers to be relatively low. Thus the evidence shows that an excess of silica in the lung tissue does not decrease the incidence of pulmonary tuberculosis. Probably those afflicted with silicosis are more liable to contract tuberculosis, as the damaged tissue hinders the reparative process.

EXCRETION OF SILICON IN THE URINE

No quantitative determinations of silica in the urine of tuberculous subjects have been reported. Such analyses might show the retention of this substance in the body, which would make probable its use in

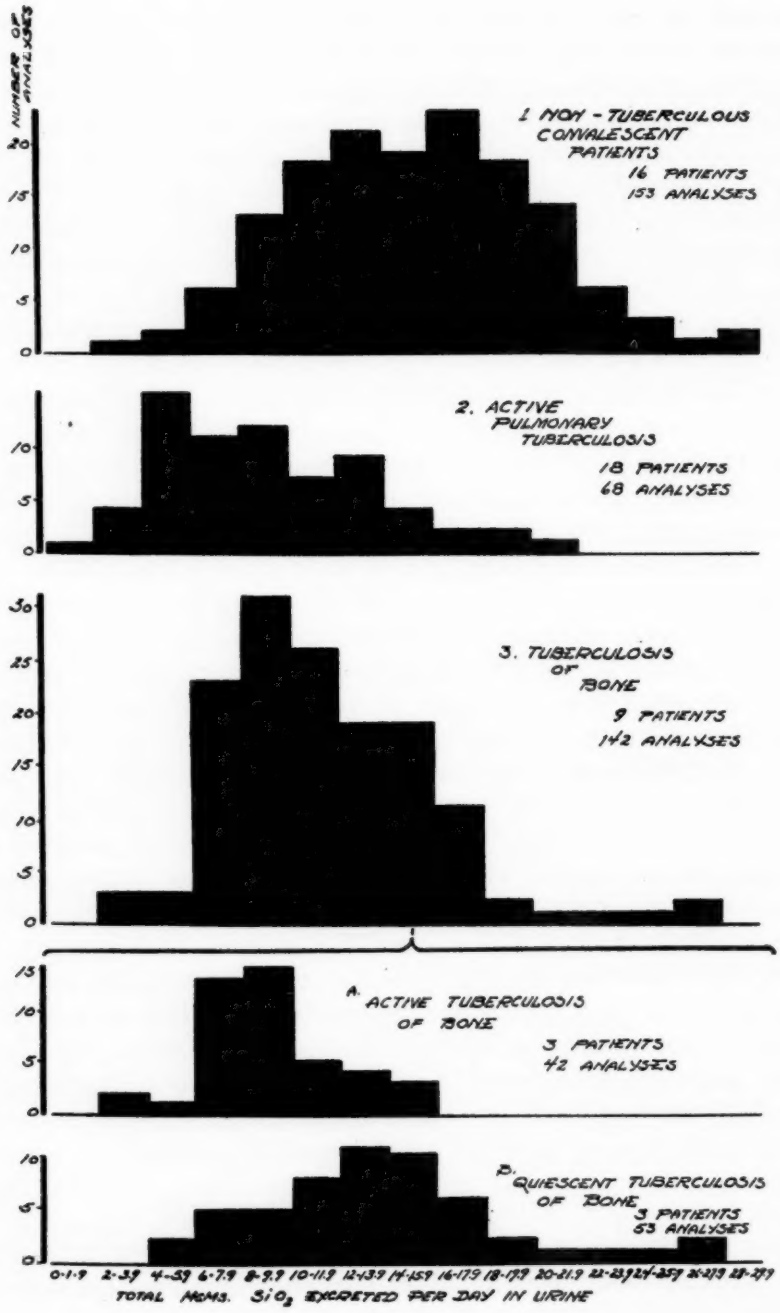
NUMBER OF ANALYSES
1. NON-TUBERCULOUS CONVALESCENT PATIENTS
16 PATIENTS
153 ANALYSES
2. ACTIVE PULMONARY TUBERCULOSIS
18 PATIENTS
68 ANALYSES
3. TUBERCULOSIS OF BONE
9 PATIENTS
142 ANALYSES
A. ACTIVE TUBERCULOSIS OF BONE
3 PATIENTS
42 ANALYSES
B. QUIESCENT TUBERCULOSIS OF BONE
3 PATIENTS
53 ANALYSES
0-1·9 2-3·9 4-5·9 6-7·9 8-9·9 10-11·9 12-13·9 14-15·9 16-17·9 18-19·9 20-21·9 22-23·9 24-25·9 26-27·9 28-29·9
TOTAL MGMS. SiO_2 EXCRETED PER DAY IN URINE

PLATE 1

connective tissue for the encapsulation of the diseased focus. The metabolism of silicon is but poorly understood. The factors which influence its absorption from the gastrointestinal tract and its elimination through the kidney, and, possibly, the large intestine, are not clear. The output of silica in the urine of an adult on the usual refined diet was found to range from 15 to 20 mgm. per day by King, Stantial and Dolan. A low value for its excretion in the urine might signify either a poor resorption of this substance from the gastrointestinal tract or its retention within the body. Silica has been demonstrated in the ash of all animal tissues and has usually been considered an accidental contaminant.

Determinations of the content of silica in the urine were made in three groups of male patients: (1) those with active pulmonary tuberculosis, (2) those with tuberculosis of bone, and (3) convalescent patients with no evidence of a tuberculous infection. All these patients were taking the regular ward-diet, with extra nourishment for those with tuberculosis. The colorimetric method described by King and Stantial was employed in these determinations. The samples of urine were collected in paraffin-lined flasks.

The mean silica content of 68 twenty-four-hour samples of the urine of 18 patients with active pulmonary tuberculosis was 9.15 $\pm$0.32 in contrast with the mean value of 11.48 $\pm$0.24 mgm. yielded by 142 similar samples from 9 patients with tuberculosis of the bone. The mean 24-hour urinary excretion of 16 patients with no evidence of recent tuberculous infection was 15.92 $\pm$0.25 mgm., as determined from the analysis of 153 samples. A further study of the results on 51 samples from three of the patients with tuberculosis of bone, whose lesions were clinically quiescent, revealed a mean excretion of 13.35 $\pm$0.46 mgm., while the mean of the findings on 42 samples from three patients with quite active bone lesions was 9.05 $\pm$0.30 mgm.

CONCLUSIONS

A comparison of these mean values, taking into account their respective probable errors, demonstrates the following:

1. The daily urinary output of silica by convalescent nontuberculous patients was significantly higher than that of patients with either pulmonary tuberculosis or tuberculosis of bone.

2. The daily urinary output of silica on the part of patients with active tuberculosis of bone did not differ significantly from that of patients suffering from active pulmonary tuberculosis.

3. A significant and progressive decrease in the magnitude of urinary silica excretion was demonstrated by groups of patients representing, respectively, quiescent, moderately active and rapidly progressive tuberculosis of bone.

BIBLIOGRAPHY

CUMMINS, S. L., AND WEATHERALL, C.: Effects of colloidal silica upon the growth of tubercle bacilli in blood, Brit. J. Exp. Path., 1931, xii, 245.

CUMMINS, S. L., AND WEATHERALL, C.: The effects of colloidal silica on experimental tuberculosis in guinea pigs, J. Hyg., 1933, xxxiii, 295.

FORSTER, J.: Die Kieselsäuretherapie der Lungentuberkulose, Tuberkulose, 1929, ix, 118.

FRANK, A.: Klinische und experimentelle Beiträge zur Frage der Kieselsäuretherapie bei Tuberkulose, Beitr. Klin. Tuberk., 1923, lv, 470.

FREUND, A.: Zur Kieselsäure behandlung der Lungentuberkulose, Ther. Gegenw., 1924, lxv, 107.

GARDNER, L. U.: Reactivation of healing primary tubercles in lung by inhalation of silica, etc., Amer. Rev. Tuberc., 1929, xx, 833.

GERHARTZ, H., AND STIEGEL: Über Lungensteine und Kieselsaürebehandlung, Beitr. Klin. Tuberk., 1908, x, 33.

GREENBURG, L.: Dust, fumes and smoke and their relation to health, Alexander's Colloid Chemistry, i, p. 865.

HACKMANN, C.: Über den Kieselsaüregehalt pneumokoniotischen Lungen, Beitr. path. Anat. u. allg. Path., 1933, xc, 623.

HAYHURST, E. R., KINDEL, D. J., NEISWANDER, B. E., AND BENNETT, C. D.: Silicosis with low incidence of tuberculosis, J. Indust. Hyg., 1929, xi, 228.

HELBACH, H.: Das Silcasin in der Behandlung der offenen Kindertuberkulose, Ztschr. Tuberk., 1927, xlix, 33.

HELWIG: Die Bedeutung der Kieselsäure für Phagocytose und Wundherlung, Ztschr. Balneol., 1914, vii, 303.

HOFFMAN, F. L.: Mortality from respiratory diseases in dustry trades, U. S. Bur. Labor Statistics, Bull. 231, Wash., D. C., 1918.

Editorial: Does silicon have a physiologic significance? Jour. Am. Med. Assoc., 1919, lxxiii, 1770.

JUNKER, F.: Kieselsäurebehandlung der Lungentuberkulose mit Silcasin, Med. Klin., 1927, xxiii, 21.

KAHLE, H.: Einiges über den Kieselsäurestoffwechsel bei Krebs und Tuberkulose und seine Bedeutung für die Therapie der Tuberkulose, München med. Wchnschr., 1914, lxi, 752.

KESSLER, A.: Zur Frage der Kieselsäuretherapie bei Lungentuberkulose, Deutsche med. Wchnschr., 1920, xlvi, 239.

KETTLE, E. H.: The demonstration by the fixation abscess of the influence of silica in determining B. tuberculosis infection, Brit. J. Exp. Path., 1924, v, 158.

KETTLE, E. H.: Experimental silicosis, J. Indust. Hyg., 1926, viii, 491.

KING, E. J., AND STANTIAL, H.: Micro-determination of silica, Biochem. J., 1933, xxvii, 990.

KING, E. J., STANTIAL, H., AND DOLAN, M.: Presences of silica in tissues, Ibid., 1933, xxvii, 1002.

KLARE, K., AND BUDDE, O.: Zur Kieselsäuretherapie der kindlichen Tuberkulose, München med. Wchnschr., 1922, lxix, 741.

KRAMER, S. P.: Über die Herstellung von Oelemulsionen mit Hilfe kolloider Kieselsäure und deren Beziehungen zu tuberkulösen Processen, Kolloid Ztschr., 1922, xxxi, 149.

KRAUT, H.: Über den Kieselsäuregehalt des menschlichen Blutes und seine Veränderung durch Kieselsäurezufuhr, Ztschr. physiol. Chem., 1931, cxciv, 81.

KÜHN, A.: Zur Behandlung der Lungentuberkulose mit Kieselsäure, Münchn. med. Wchnschr., 1918, lxv, 1459.

LADENDORFF: Über Änderungen des Blutdruckes bei Lungentuberkulösen, Ztschr. Balneol., 1912, v, 159.

MAVER, M. E., AND WELLS, H. G.: The chemical composition of calcified tuberculous lesions, Amer. Rev. Tuberc., 1922, vi, 649.

MOORE, B.: The incidence of industrial tuberculosis, Proc. R. Soc. Med., 1918, xi, 145.

MCNALLY, W. D.: Silicon dioxide content of lungs in health and disease, Jour. Amer. Med. Assoc., 1931, ci, 584.

PRICE, R. M.: Effect of silica on growth of tubercle bacillus, Proc. Soc. Exp. Biol. & Med., 1931, xxviii, 819.

ROSENSTINGL, A.: Zur Bewertung der Kieselsäurezufuhr in der Phthiseotherapie, Beitr. Klin. Tuberk., 1929, lxxiii, 110.

RÖSSLE, R.: Zur Siliziumbehandlung der Tuberkulose, München. med. Wchnschr., 1914, lxi, 756.

ROTH, M.: Zur Frage der Kieselsaürebehandlung bei Lungentuberkulose, Ther. Gegenw., 1921, lxii, 369.

SCHEFFLER, L., SARTORY, A., AND PELLISSIER, O.: Les injections intraveineuses de silicate de soude, Presse Méd., 1920, xxviii, 806.

SELKIRK, W. J. B.: Tuberculosis in limeworkers, Brit. M. J., 1908, ii, 1493.

SCHULZ, H.: Ueber den Kieselsäuregehalt menschlichen Bauchspeicheldrüse mit Bermerkungen über die Gewichtsverhältnisse der Drüse in den verschiedenen Lebensaltern, Biochem. Ztschr., 1915, lxx, 464.

SCHULZ, H.: Über den Kieselsäuregehalt menschlichen und thierischer Gewebe, Pfluger's Arch ges. Physiol., 1901, lxxxiv, 67.

DE SCHWEINITZ, E. A., AND DORSET, M.: The mineral constituents of the tubercle bacillus, Centralb. Bacteriol., 1898, xxiii, 993.

SALOMON, P.: Beitrag zur Kieselsäuretherapie, Aertzl. Rundschau, 1927, xxxvii, 212.

STEIN, W.: Zur Kieselsäuretherapie der Bronchialdrüsentuberkulose, Ztschr. Tuberk., 1921, li, 377.

THOMA, E.: Experimentelle und klinische Beobachtungen zur Kieselsäuretherapie bei akuten und chronischen Infektionskrankheiten, München med. Wchnschr., 1922, lxix, 1603.

ZELLER, H.: Erfahrungen mit Silistren, Therap. Gegenw., 1922, lxiii, 38.

ZICKGRAF: Ueber die therapeutische Verwendung der Kieselsäure und über die Beteiligung der Kieselsäure an der Bildung von Lungenstein, Beitr. Klin. Tuberk., 1906, v, 399.

ZIMMER, G.: Silicum als Reizmittel, München. med. Wchnschr., 1923, lxx, 233.

NONTUBERCULOUS PULMONARY DISEASE SIMULATING TUBERCULOSIS IN CHILDREN[1]

CHRISTIAN W. NISSLER, MARTIN J. SOKOLOFF AND LOUIS COHEN

The diagnosis of latent, childhood or primary tuberculosis in children is made chiefly by the X-rays and the tuberculin test. The accuracy of the latter has been established in the studies by Opie (1), Hetherington (2), Rigler and Exner (3), Hart (4), Myers (5), Fishberg (6), Stewart (7), and others, and is further substantiated by the work of Blocklock (8) and Gohn (9) that the positive skin tests are as significant in the diagnosis as the finding of tuberculous lesions at autopsy.

Krause (10) states that the allergic state can come into play within two weeks, more or less, after the first focalization of tubercle bacilli within the body. All later tissue effects must be regarded as being variably influenced and moulded by allergy.

The allergic state (tissue allergy) in tuberculosis is, as is well known, a concomitant of establishment of focal tubercle, be the latter the product of tissue reaction to the living or dead tubercle bacilli. The smallest number of living bacilli, if they survive in the body, will infallibly lead to tissue allergy, and, with certain well-understood reservations, allergy will persist as long as bacilli remain. The intensity of allergy rises wth the extension or progression of the tuberculous infection. At the present time we may take the position that all animals with tubercle acquire allergy and tuberculoallergy does not exist in the absence of focal tubercle.

In epituberculosis, there is a more or less extensive exudative or atelectatic involvement of the lung, with which the child may or may not show any marked illness, though in the majority of cases there are few or no symptoms. The involvement is usually of the upper lobe. The temperature is usually normal or may have marked elevation. The signs may be absent, as in our case, or may have slight decrease in expansion of the chest on the affected side, decrease in fremitus, an impairment on percussion and distant breath-sounds. In one case,

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L. F., age 11, signs were absent, and the involvement was in the right upper lobe. The X-ray study (November 7, 1932) showed partially calcified lymph nodes in the right hilum region. There was an area of moderately dense consolidation lying in the midclavicular line at the level of the third rib anteriorly. On March 29, 1933, the area had completely resolved and the tracheobronchial lymph nodes, especially the upper right, showed considerable calcareous deposits.

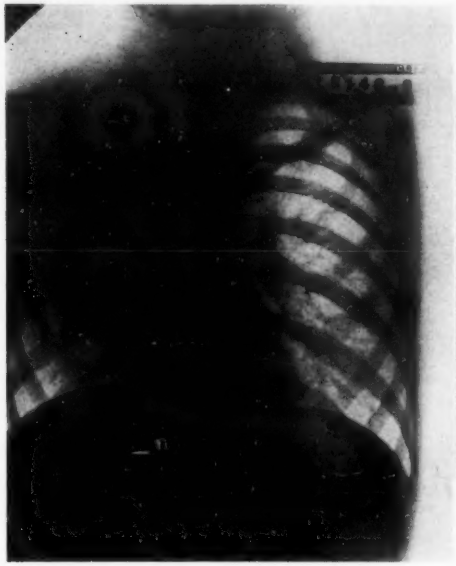
Stewart (7) found that lesions due to various nontuberculous conditions in general do not differ greatly from those found in tuberculin-positive children except that those who had positive tuberculin reactions had a greater relative frequency to pleural thickening. McPhedran (11) in his studies found that chronic infectious, nontuberculous pulmonary lesions generally predominate on the left side in the lower lobe and are often bilateral. Stewart (7) found, in his observations of eleven years of follow-up study, that the primary infection, due to tubercle bacilli, in children with extensive parenchymal lesions, resolves and disappears, or leaves inconspicuous calcified areas, though it may take many months to do so; whereas in the secondary infection, adult type, due to reinfection (whether exogenous or endogenous), the mortality rate has been high and the lesions tend to spread and cavitate. The prognosis is grave in the adult type of tuberculosis. This type of tuberuclosis frequently results in death, while the primary infections are seldom fatal. Mayer (12) states that 90 per cent are positive for tubercle bacilli when cavitation is due to tuberculosis, but that negative sputa should not be accepted until gastric contents have been examined for the tubercle bacilli.

Owing to the distribution of the lesions of our 3 cases such conditions as these are not infrequently diagnosed as pulmonary tuberculosis. No further attempt is made to determine the cause, and the diagnosis is allowed to remain as such. The 3 children were diagnosed as having pulmonary tuberculosis by the positive tuberculin reactions and X-ray studies. The X-ray studies showed the lesions in each case to be in the upper lobe and unilateral.

Case 1: A young white girl, M. M., age 10, whose chief complaint was cough since September, 1932 with a slight amount of mucoid but not bloody sputum, was unable to gain weight and had dull pain on coughing and shortness of breath on exertion. *Family history:* There was no history of tuberculosis in the family. The patient has three sisters and one brother living and well. Her father has nephritis. *Personal history:* She had had measles. Present

illness: The patient always enjoyed fairly good health until September, 1932, when she contracted pneumonia. She was confined to bed for about six weeks; then was well for about ten days and had a recurrence of pneumonia in October. She was taken to a hospital, where she was kept in bed for about five weeks. She had a dull pain in her chest with it; her cough was productive at times and again dry. She was referred to the City Chest Clinic with a diagnosis of pulmonary tuberculosis. On her admission to the Chest Clinic on March 2, 1933, she was a sick child. Her temperature was 99°F., pulse 120, and respirations 20. *Physical examination:* The upper respiratory tract was negative. The right side of the chest was flattened, expansion was limited in the upper right half; there was increased tactile fremitus, dulness on percussion, and bronchial breath-sounds with medium-sized crackling râles, and whispering pectoriloquy was present. A diagnosis of consolidation was made. The X-ray study showed atelectatic pneumonic consolidation involving the right upper lobe, with moderate tracheobronchial adenitis with shifting of the great vessels, heart and trachea to the affected side. The intracutaneous tuberculin test was positive. Sputum examinations were negative for tubercle bacilli. The patient was referred to the Bronchoscopic Clinic of Jefferson Hospital on April 1, 1933, and Dr. Louis Clerf made a bronchoscopic study. A partial stenosis of the right upper bronchus was found. A small amount of secretion was obtained from which a smear and cultures were made. One culture was positive for *Staphylococcus albus* and *Streptococcus haemolyticus*. The culture for tubercle bacilli on June 12, 1933, was negative, as was the smear. During the summer she was a patient at a preventorium for four months where she derived some benefit, although the clinical findings did not show any marked improvement. The patient returned to school and the school physician sent her to another clinic, where, from the X-ray study, a diagnosis of pulmonary tuberculosis was made without sputum examinations. She returned to the City Chest Clinic and was from there referred to the Bronchoscopic Clinic on January 16, 1934. An X-ray study on January 16th showed that there was less density than on the first admission, although the heart and vessels were pulled over more to the affected side. Three sputum examinations in January and February were negative for tubercle bacilli. On March 22nd a bronchoscopic study was done and secretion from the right upper bronchus was obtained for culture and smears. The bronchus remained narrowed. The smear was negative for tubercle bacilli on March 26, 1934 and the culture was also negative. In July, tissue was procured from the right upper bronchus and histological study revealed it to be granulation tissue.

This could have been of the initial or childhood-type infection, but, owing to the history of pneumonia, repeated negative sputum examina-



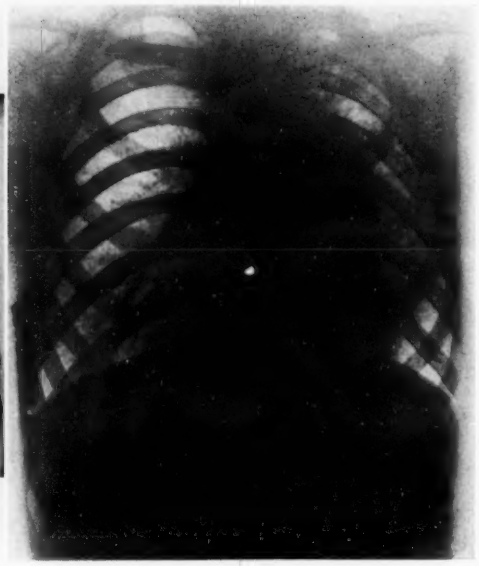


Fig. 1 Fig. 2 Fig. 3

Fig. 1. (Case 1.) Atelectatic pneumonic consolidation, right upper lobe, with shifting of heart, great vessels and trachea to affected side.

Fig. 2. (Case 2.) Congenital cysts of lung. Lipiodol injection in roentgenogram on the right.

Fig. 3. (Case 3.) Shows considerable fibrosis of left upper lobe with cavitations. The mediastinum and trachea are drawn to the left

tions for tubercle bacilli, the negative cultures for tubercle bacilli, negative smears from secretions obtained through the bronchoscope and the positive sputum culture of *Staphylococcus albus* and *Streptococcus haemolyticus* and tissue study from a stenosed area of bronchus showed this to be granulation tissue without evidence of tuberculosis, it is concluded that these findings contradict the impressions obtained from the X-ray study and the positive tuberculin test. Then, too, the slow process of resolution of the involved upper lobe is contrary to that of latent or childhood type of tuberculosis. The atelectasis appears to be from bronchial obstruction due to organisms other than the tubercle bacilli causing the granulation tissue. The principle intrabronchial causes for atelectasis, elaborated upon by Funk (13), are foreign-body, primary new growths, bronchial inflammations with ulceration and exuberant granulations, inspissated secretions, postinflammatory cicatricial contraction and web-like formation. Norris and Landis (14) stress inflammatory conditions, such as bronchitis, bronchopneumonia and whooping-cough, as causes.

Case 2: A male, J. V., age 11, was admitted to the clinic as a contact case. His chief complaint was occasional cough. *Family history:* His sister has been diagnosed as having pulmonary tuberculosis, April 10, 1926. *Personal history:* He had pneumonia in infancy and measles but no other illnesses. On admission to the clinic September 20, 1928, one of us (2) on physical examination found a flat chest, delayed expansion in the upper right with increased fremitus, tympany on percussion, and bronchial breathing with many course crackling râles and whispering pectoriloquy. The left lung was clear. The sputum studies were negative. The boy was sent to a sanatorium, where he was from December 3, 1928 to July 25, 1931. On his return the physical examination showed no changes from that on admission. He was 11 per cent underweight. The temperature averaged 99°F., respirations 20, pulse 108. The Mantoux test was positive. On his return from the sanatorium the question of artificial pneumothorax was entertained and he was referred to the hospital for further study. An X-ray study was made, and the question of congenital cysts of the right lung was raised. Bronchoscopic study was done, and secretion from the bronchus of the right upper lobe was obtained; smears and cultures were made and guinea pig innoculation was done. All were negative for tubercle bacilli. Lipiodol was injected into the right bronchus, and in figure 2 may be seen the outline of the cysts very clearly. Repeated studies of sputum for tubercle bacilli were negative over a period of five years.

The second case with a diagnosis of congenital cyst of the lungs, being a contact case, with the tuberculin test positive and X-ray confirmation of tuberculosis, would give at first the impression of pulmonary tuberculosis. The signs of cavities in the right upper lobe on the first examination, with no marked change in the involved area in six years of observation, are a factor in aiding the elimination of tuberculosis of the lung, for lesions of the adult type of tuberculosis tend to spread and cavitate, and the prognosis is grave. If this represents the adult type of tuberculosis, or secondary infection over a period of six years with cavitation, one would think that the spread of infection would pass to the other lobes of the same lung or would have a bilateral involvement. With negative findings for the tubercle bacilli and the injection of lipiodol displaying the cystic cavities, we are safe in assuming that the condition is nontuberculous.

Norris and Landis (14) regard the condition of cysts as rare in the American literature. Eloesser (15) reported 4 cases. (Our case is one of multiple small cysts.) A whole or one part of the lobe may be involved. Congenital cystic disease may persist into adult life. Stewart, *et al.*, (16) report a case of an adult female, age 54, who came to autopsy with multiple congenital cysts. She had been diagnosed as having pulmonary tuberculosis in three different hospitals.

The third patient has a most unusual history, one of massive infections in infancy and early childhood.

Case 3: A male, A. K., white, age 7, was admitted to the City Chest Clinic with a diagnosis of pulmonary tuberculosis. The chief complaint was of cough with sputum. *Family history:* His mother died of pulmonary tuberculosis. *Personal history:* He had rickets when admitted to the Hospital at the age of 3, May 7, 1921, and showed malnutrition and neglect. He was suffering from acute tuberculous osteomyelitis involving the left and right feet, with purulent discharge from the left infraorbital bone. He developed a cold abscess in the left popliteal space. In August of that year he had involvement of the middle finger of the left hand. On admission to the Hospital he had signs of meningitis; the spinal fluid examination on May 20th showed no tubercle bacilli. There was no growth after some days. The Pirquet test was positive. The blood-Wassermann test was negative. The child had tuberculosis of the skin of the feet, legs and arms. On December 18, 1921, he was found to have diphtheria, and was sent to the Municipal Hospital. In the course of three years he was admitted to the Philadelphia General Hospital four times for his tuberculous osteomyelitis. He had a

retropharyngeal abscess in June, 1922. On August 17, 1923, he had signs of meningitis, and was in a comatose state. Smears from the draining sinus of the left infraorbital bone on July 31, 1922, were negative for tubercle bacilli. On June 10 of 1924 he had a tonsillectomy. In January, 1925 he had measles. The child was admitted to the Clinic on August 23, 1927, with a diagnosis of pulmonary tuberculosis. The blood-Wassermann test was negative. He complained of a productive cough. The temperature averaged 98.4°, pulse 76, respirations 20. The physical examination revealed scars on his neck from previous abscesses, which he had had from the time he left the hospital following tonsillectomy, to his admission to the hospital for tuberculosis of the lungs. He had many scars on his feet, legs, hands and face from previous tuberculous osteomyelitis. The physical examination of the chest showed a slightly deformed chest with the upper left flattened. The thorax showed the signs of rickets. The expansion was delayed on the left side, with increased tactile fremitus and dulness over the left upper lobe. There were bronchial breathing and râles, fine and crepitant in character. The Mantoux test was positive. In August, 1928, he was sent to a sanatorium where he remained until June, 1929. The physical examination showed no marked changes from the first examination in 1927. The sputum examinations have been repeatedly negative. The X-ray of December, 1933, showed considerable fibrosis of the left upper lobe. There are multiple cavities; the trachea and mediastinum are drawn to the left. The right lung appears to be normal. The bronchoscopic report was that the lesion may have been tuberculous, although it was not possible to find anything to substantiate this belief. Secretions from the left upper bronchus were negative for tubercle bacilli in culture and smears.

The third case has pulmonary fibrosis. Fibrosis (19) can come from almost any disease to which the lung is subject, whether acute or chronic.

The child was a contact case, he had multiple areas of tuberculous osteomyelitis over a period of three years and tuberculosis of the skin, and he reacted positively to tuberculin. Retropharyngeal abscess and tonsillectomy could have been factors in causing pulmonary fibrosis. The physical findings in his left upper lobe did not change to any appreciable extent in seven years and repeated sputum examinations were negative. Bronchiectasis may follow fibrosis, and it is a question whether these cavities are bronchiectatic in origin. The Wassermann test was negative. When conditions, such as fibrosis or cavities, are due to tuberculosis, the tubercle bacilli are usually found in the sputum and there may be signs of disease in the other lung. Blocklock (8), in 6 cases of tuberculosis of the bones, found the caseous lesions secondary to

primary thoracic tuberculosis in 4 children and in two were with a primary abdominal lesion. The direct method of obtaining secretions by bronchoscopic method with negative cultures and smears would rather favor the causative factor being from one of the other infections, such as retropharyngeal abscess or following tonsillectomy.

COMMENT

The 3 patients each had positive tuberculin reactions. The allergic state (tissue allergy) in tuberculosis is, as is well known, a concomitant of establishment of focal tubercle, be the latter the result of tissue reaction to living or dead tubercle bacilli. The X-ray studies suggested tuberculosis. The history of such long-standing involvement with little or no appreciable changes would rule out epituberculosis, for in the latter the duration is only a few months, whereas in these three patients the involvement has been from two to seven or more years. The 3 cases have been repeatedly negative for tubercle bacilli in smears from the sputum; guinea-pig innoculations have been negative; and culture studies have been negative in two cases. The sputum cultures were obtained by bronchoscopy. Two patients had cavitation over a period of years of clinical observations and X-ray studies, and there has been no spread to the other lung. The general impression is that primary infection, whether severe or not resolved, disappears or shows inconspicuous calcified areas, whereas in secondary infection the mortality rate is high, the lesions tend to spread and cavitate, the prognosis is grave, and death not infrequently results.

Our 3 cases have been contrary to all such findings and observations, as those of primary and (adult-type) secondary infection of tuberculosis, and we are of the opinion that the lesions in the chests of these 3 cases reported are nontuberculous.

CONCLUSIONS

1. Nontuberculous lesions can be in the upper lobe and unilateral.
2. A child may have a positive tuberculin test and X-ray findings suggesting tuberculosis, yet have no positive tuberculous lesions.
3. A careful history is of the utmost importance, as are clinical observations, and X-ray and repeated laboratory studies.
4. Careful study of the sputum, gastric-lavage contents, the use of sputum in making cultures, guinea-pig inoculations and smears are of great aid in the differential diagnosis.

5. Bronchoscopic studies are of great value in doubtful cases in which the sputum is repeatedly negative, for in this way secretions may be obtained directly from the foci free of contamination, and the method also provides direct visualization of the bronchi.

Note: We wish to thank Dr. Louis Clerf of Jefferson Hospital for his great help on two of our studies and Dr. Chevalier Jackson of Temple University Hospital for his aid in one study, which made it possible for us to come to a diagnosis in the cases presented. We also wish to thank Dr. Carl Bucher for making the laboratory examinations.

REFERENCES

(1) Opie, E. L.,Landis, H. R. M., McPhedran, F. M., and Hetherington, H. W.: Tuberculosis in public school children, Amer. Rev. Tuberc., 1929, xx, 414.
(2) Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: Ibid., 1929, xx, 437.
(3) Rigler, L. G., and Exner, F. B.: The latent period in roentgen-ray diagnosis of pulmonary tuberculosis, Jour. Am. Med. Ass., 1934, cii, 1750.
(4) Hart, P. D.: Medical Res. Council, Special Report Series, 164, 1932.
(5) Myers, J. A.: Ann. Int. Med., 1932, vi, 672.
(6) Fishberg, M.: Pulmonary tuberculosis, Phila., Lea & Febiger.
(7) Stewart, C. A.: Evolution of tuberculosis in the human lung, Am. J. M. Sc., 1933, clxxxv, 346.
(8) Blocklock, J. W. S.: Tuberculous disease in children, Medical Research Council, Privy Council, Special Report no. 172, 1932, London.
(9) Gohn, A.: Berlin, Schwarzenberg, 1912.
(10) Krause, A. K.: Amer. Rev. Tuberc., 1927, xv, 137.
(11) McPhedran, M. F.: Tuberculosis in public school children, Ibid., 1929, xx, 4.
(12) Mayer, E.: The cavity in tuberculosis, Jour. Am. Med. Ass., 1933, c, 1478.
(13) Funk, E. H.: Diagnosis and treatment, Oxford Monographs, v, 138, Oxford Press.
(14) Norris, G. W., and Landis, H. R. M.: Diseases of the chest, ed. 5, Saunders, 544.
(15) Eloesser, L.: Surgery, Gynecol., & Obst., March, 1931.
(16) Stewart, H. K., Kennedy, P. J., and James, A. E.: Congenital cyst of the lung, Arch. Pathol., 1932, xiv, 627.
(17) Oslers Principles and Practice of Medicine, ed. 11, p. 648, Appleton.
(18) Stewart, C. A.: Does primary tuberculous infection afford adequate protection against consumption, Jour. Am. Med. Ass., 1933, c, 1077.
(19) Norris, G. W., and Landis, H. R. M.: Diseases of the chest, ed. 5, p. 536, Saunders.

CALCIUM METABOLISM AND TUBERCULOSIS[1]

VITO VETTOR PISANI

It is now generally recognized that the physiological activities of the body depend upon certain minute chemical changes that take place in the tissue cells. Hence an ideal of health may be said to consist in a perfect biochemical balance in the tissues, and disease, on the other hand, should be looked upon as the resultant of changes which disturb this biochemical balance. Such a physiological and chemical equilibrium is largely maintained by certain minerals of the body.

The capacity of the tissues to adapt themselves to new conditions and environment and to resist infection also depends upon those minerals found normally in the tissue cells. What are these minerals that play such a vital rôle in health and disease? The most important are sodium, potassium, calcium and magnesium. These elements are divided into two groups or pairs on account of their antagonistic physiological activities: namely Na/K and Ca/Mg. Thus the Na/K group encourages capillary permeability, while the Ca/Mg group decreases it; the Na/K group stimulates the sympathetic system, while the Ca/Mg group inhibits its activity; the Na/K group tends to disperse colloids, while the Ca/Mg tends to aggregate them. The Na/K group encourages liquefaction of tissues, while the Ca/Mg tends to coagulate them. It is quite evident then that these minerals, under normal conditions, counterbalance each other in their physiological effects.

In studying the metabolism of these minerals we observe that the metabolism of calcium stands out rather prominently and that some of its phases are unique in their characteristics and peculiarities.

We may say incidentally that the interest in calcium metabolism appears to advance in cycles. There have been similar waves of interest in nitrogen metabolism, in carbohydrate metabolism, in the basal-metabolic rate, and it has been within the last few years that there has been a markedly increased interest in calcium metabolism.

Such unusual interest is explained by the fact that calcium is an

[1] Presented at a meeting of the Medical Staff of the Chicago Municipal Sanitarium, Chicago, Illinois, December 12, 1934.

element absolutely necessary to life and is present in the body as an integral part of every living cell and tissue, participating, as far as we know, in all physiological processes of all organs:

1: The very rhythmic contraction of the heart depends mainly upon the interaction between Ca and K.
2: Calcium figures prominently in the physiology of nerve impulses, and it is necessary for the transferring of nerve impulses at neuromuscular junctions as well as from one neuron to another.
3: Calcium contributes its share in the maintenance of acid-base equilibrium.
4: It is indispensable in the processes of coagulation and fibrosis.
5: The normal state of irritability of striated muscles depends on calcium.
6: In inflammation it tends to check certain inflammatory changes which are deleterious to normal cell-function.
7: It stimulates phagocytosis.
8: Of course the most obvious function of calcium is that of bone-formation.

This brief enumeration of the physiological activities of calcium serves to indicate the important rôle that this mineral plays in the animal economy, and a review of the newer studies made upon calcium metabolism will, no doubt, help us to understand better the vital part played by this element both in health and in disease.

Calcium metabolism may be logically divided into four stages, namely, (1) calcium intake, (2) calcium absorption, (3) calcium retention and (4) calcium elimination or dispersion.

We will not spend much time in discussing *calcium intake*, which deals with foods and their calcium content. We wish only to point out the fact that our modern American diet is usually deficient in calcium. The studies of Sherman prove that. It appears that such a deficiency is due to the abundant use of meat and carbohydrates.

The second stage of calcium metabolism deals with the *absorption* of calcium. The calcium of the diet is absorbed from the gastrointestinal tract into the blood. From this circulating fluid it passes into the tissue cells, where calcium may be retained if needed, or it may be returned to the circulation and eventually excreted through the bowels and kidneys.

Calcium absorbed from the gastrointestinal tract reaches the blood partly in diffusible and partly in nondiffusible form. The absorption of the diffusible fraction of calcium depends upon the chemical reactivity of free hydrochloric acid of the gastric juice, while the absorption of the nondiffusible fraction depends upon the solvent action of the bile-acids.

It is important to state here that calcium compounds ingested with food are usually either slightly soluble or not soluble at all. Those soluble are converted by the action of the hydrochloric acid of the gastric juice into $CaCl_2$. This represents the diffusible fraction of blood-calcium, which is, in part, ionized, and the other part is not ionized. Whatever portion of the calcium salts is not absorbed in the upper part of the intestinal tract, in reaching the alkaline content of the lower bowel, precipitates in the form of carbonates and phosphates, and, in the presence of fatty acids, precipitates as calcium soaps. These insoluble calcium salts are not all ejected as such, but some of them are absorbed through the solvent action of bile acids.

The ionized fraction of calcium is chemically active and necessary for the various vital processes of the body. The nonionized fraction is utilized for the coagulation of the blood. It is well to mention here that in spite of the fact that calcium estimation may indicate a normal calcium level of the blood, there may nevertheless be a lack of either ionized or nonionized calcium.

The normal absorption of calcium does not depend solely upon a sufficient supply of calcium salts and a necessary amount of free hydrochloric acid, but also upon a certain amount of phosphates present in the food ingested. A deficiency of phosphates leads to an insufficient absorption of calcium. There is a certain definite proportion between calcium and phosphorus absorption which is regulated by vitamine D. How vitamine D regulates calcium and phophorus metabolism is still unknown to us.

We readily see then that the mere administration of calcium for therapeutic purposes does not ensure a necessary supply of calcium for body use, unless phosphates and vitamine D are also present in adequate amounts in the diet, and even then the absorption of calcium may be insufficient if there is a diminution in free hydrochloric acid of the gastric juice.

The vital issue hangs not so much upon the amount of calcium ingested and the amount of calcium absorbed, as it does upon the amount of calcium which is *retained* by the tissues for the necessary requirements of the body, and, to be sure, calcium therapy is intimately related with calcium retention.

While it is true that, in cases of insufficient calcium intake or calcium absorption, the blood replenishes itself with this mineral from the trabeculae of the epiphyseal ends of the long bones, this draining process

cannot go on forever. Under normal conditions not a day passes by without calcium flowing to and from the epiphyseal ends of the long bones. When the diet is rich in calcium the blood retains whatever amount the body needs and the rest is deposited in the bones, and, contrariwise, when the diet is poor in calcium the blood replenishes itself by withdrawing calcium from these storehouses.

Calcium retention: Calcium retention is influenced mainly by (1) certain glands of internal secretion, (2) the alkalinity of the blood, and (3) the amount of blood-phosphorus.

The glands of internal secretion regulating calcium metabolism are divided into two groups—the anabolic and the catabolic.

The anabolic group consists of (1) thymus, (2) anterior portion of the pituitary gland, and (3) the suprarenal cortex. An increased activity of these glands causes an increase of calcium retention.

The catabolic group consists of (1) thyroid and (2) suprarenal medulla. The hyperactivity of these glands leads to an increased dispersion (1).

The parathyroids, although falling into the anabolic group, have a regulatory function and a definite level of blood-calcium is maintained by their activity.

Alkalinity of the blood: It appears that calcium retention is diminished by reducing the alkalinity of the blood. The end-products of protein metabolism are acid and give a continuous source of acid radicles to be eliminated. It is partly in the neutralization of these acid metabolites that the metabolism of calcium becomes of interest.

Blood phosphorus: The retention of blood calcium depends also upon the amount of phosphorus circulating in the blood. An excessive amount of one of these two minerals will cause elimination of the other; therefore, in case of hyperphosphataemia there is an associated hypocalcaemia, and *vice versa.*

Elimination of calcium: Elimination of calcium depends upon a number of factors, some of which have already been mentioned, as, for instance, (1) high blood-phosphorus, (2) a high protein diet leading to a production of a large amount of acid metabolites, (3) reduction of blood alkalinity due to disease or otherwise, (4) disturbances in the glands of internal secretion regulating calcium metabolism, as, for example, hyperthyroidism, or (5) lack of vitamine D. Any one of these conditions causes calcium dispersion, resulting in calcium deficiency, in spite of the fact that the evaluation of blood-calcium may indicate no abnormal deviations.

CALCIUM IN TUBERCULOSIS

With this rapid presentation of calcium metabolism and with the intimation of the various problems and difficulties found intimately connected with calcium metabolism, I hope to have made one point clear, and that is that the absorption and retention of calcium for the needs of the body depend upon a number of factors, which may be easily disturbed by various conditions under which we live and by pathological states of the body.

Calcum metabolism is easily altered in febrile tuberculosis patients, because of denutrition, of depressed digestive processes, of deficiency in free hydrochloric acid in the gastric juice (2), of reduced alkalinity of the blood, and of increased elimination of calcium on account of exudative inflammatory processes. We wish to call attention to the fact that in all exudative lesions there is an increase of H-ion concentration in the affected tissues with a relative dispersion of calcium. This state of affairs has been demonstrated conclusively by Schade (3).

It has been proved with accurate calcium evaluation that tuberculosis patients with exudative lesions predominating do eliminate more calcium than the amount ordinarily eliminated under normal conditions (4). If this is true, then calcium deficiency is to be considered as a serious handicap for such types of patients, inasmuch as calcium plays an important rôle in the process of healing of tuberculous lesions.

It is a matter of common knowledge that the healing of a tuberculous lesion, when it does occur, is always associated with the formation of fibrous tissue. In this defense-reaction of the body we find calcium to be an indispensable element.

It is admitted that the process of coagulation, apparently of the same nature as that which occurs in clotting of the blood-plasma, constitutes the fundamental feature in the development of the fibrils arising in the ground-substance in such conditions as wound-healing and infections (5). This coagulative process depends upon certain chemical changes in which calcium is absolutely necessary. Without the action of this element the formation of fibrils would not take place any more than the coagulation of blood would occur without the presence of calcium. It is well to review rapidly the various steps of fibrosis in order to demonstrate the indispensability of calcium in the production of fibrous tissues.

As the result of inflammation, the capillaries become dilated and more permeable; hence serum and its constituents (serum-albumin, serum-

globulin and fibrinogen) pass into the paravascular spaces. Some cellular elements of the blood (white cells, red cells and platelets) also pass through the capillary wall into the paravascular spaces.

In acute inflammatory conditions this exudate is readily reabsorbed, and the tissues involved are restored to their histological integrity. In chronic inflammation, however, some of the exudate remains stagnant and the blood-cells there found are eventually disintegrated, while the protein compounds (serum-albumin, serum-globulin and fibrinogen) undergo certain chemical changes.

In the process of cellular disintegration the blood platelets liberate thromboplastin which unites with antithrombin, thereby releasing prothrombin. Prothrombin by the action of calcium salts is changed into thrombin, and thrombin combines with fibrinogen to form the insoluble compound, fibrin. It is this insoluble substance which is the *sine-qua-non* basis of the fibrous tissue of healing.

As the result of these chemical changes the exudate of the paravascular spaces is converted into 2 histological elements: (1) the ground-substance or matrix, a soft, structureless material, and (2) the fibrils, which are embedded in the ground-substance, forming a network. Eventually these fibrils will unite through a process of fusion, and form long fibrils. Afterward, these fibrils are drawn together, so that they lie parallel to each other, and thus form white waxy bundles of hard nonelastic fibres.

We can readily see, then, that calcium deficiency would, no doubt, retard the process of healing in tuberculous lesions, inasmuch as the production of fibrous tissues depends upon a chain of chemical changes in which calcium represents an indispensable link.

Notwithstanding the advance made in the study of calcium metabolism, which appears to invalidate more and more the teachings of Sergent, Ferrier and others, namely, that recalcification is quite essential in the healing of tuberculous lesions, very little combined effort has as yet been manifested by tuberculosis specialists in carrying on a rational and systematic plan of calcium therapy, as a valuable adjunct to other well-accepted therapeutic measures.

There are three main reasons why recalcification of the tuberculosis patient has not been practised universally and permanently. One of these is that we expect from calcium the miracle of a specific, overlooking the fact that the healing of a tuberculous lesion is effected through slowly evolving pathological changes, requiring many months, if not years. The second reason is that the indiscriminate and empirical employment

of this treatment leads, no doubt, to many disappointments. Recent studies have afforded a clue to the guiding principles in the selection of cases which are likely to be benefited from the administration of calcium. The fibrocaseous type ("hard lung") is not in need of lime salts, because it appears that in such a patient calcium metabolism is carried on efficiently for the necessary requirements of the body and for the healing of tuberculous lesions. The exudative type ("soft lung") is, on the contrary, in urgent need of calcium because of an excessive faecal and urinary elimination (6).

A third reason explaining the apathetic attitude toward recalcification is blood-calcium evaluation. Let us say very emphatically that the estimation of blood-calcium is extremely misleading, and should not be regarded as a guiding norm in the application of calcium therapy. In rickets or in spasmophilia, for instance, the blood-calcium may be within normal limits, yet we know beyond doubt that in such conditions we are dealing with calcium deficiency. No other factor has contributed more to the apathy toward recalcification in tuberculosis patients than blood-calcium evaluation. Noorden well said that "blood-calcium does not indicate the calcium wealth or impoverishment of the tissues where the disease process takes place."

The only scientific method that we possess at the present time is the determination of the relation between calcium-intake and calcium-output. Patients are placed on measured rations of calcium, and the faecal and urinary calcium is estimated. Under normal conditions the calcium elimination should be equal to that ingested minus about 7 grains for the bodily requirements in 24 hours. Leufar and Lematte (4) have carried out this accurate method of calcium estimation in tuberculosis patients who had active disease, accompanied by loss of weight and fever, and have found that this class of patients displayed an increased amount of urinary and faecal calcium. This is an *experimentum crucis* and should be convincing and final.

SUMMARY AND CONCLUSIONS

In closing, I should like to call your attention again to three important facts:

1. That blood-calcium evaluation is misleading and should never be employed in the determination of the calcium-content condition of the patient.

2. With a more accurate method of calcium estimation, Leufar and

Lematte have demonstrated that tuberculosis patients with exudative lesions exhibited calcium deficiency.

3. That tuberculous lesions heal only through fibrosis, and that the coagulative process, which is the fundamental feature of fibrosis, depends mainly upon the presence of calcium salts.

Aside from the foregoing considerations, calcium therapy appears to be logical in the treatment of tuberculosis because

1. It exercises a tonic effect upon the Rouget cells and thereby decreases the inflammatory oedema.

2. By supplying the tissues with a normal amount of calcium, H-ion concentration is normalized, and thus the normal osmosis is reëstablished.

3. Calcium raises the phagocytic power. This property has been demonstrated by Rosenow.

4. The cardiovascular system is also benefited by calcium administration, since it has a digitalis-like effect on the heart and kidneys.

Just a word more about calcium therapy in tuberculosis. By a careful analysis of the various conditions existing in tuberculosis, and by a thorough study of the pharmacodynamic action of calcium, it appears that the recalcification method in tuberculosis patients is scientific and sound, and should give gratifying results. It will be disappointing, however, unless we carefully select patients who display exudative lesions, associated with a mixed infection, toxaemia of relatively acute form, rapid clinical progress, and severe constitutional disturbances.

REFERENCES

(1) VINES, H. W.: The parathyroid glands in relation to disease, London, 1924.
(2) COHN, S. G.: The gastric function in pulmonary tuberculosis, Amer. Rev. Tuberc., April, 1933.
(3) SCHADE, H.: Cited by CANTAROU: Calcium metabolism and calcium therapy, 1931.
(4) LEUFAR, M.: Calcium exchange in tuberculosis, Rev. d. l. tuberc., August, 1926, vii, 600. (Also abstr. from Amer. Rev. Tuberc., 1928, xvii, 73.)
(5) BAITSELL, G. A., AND MASON, K. E.: The origin of fibrosis, Amer. Rev. Tuberc., 1930, xxi.
(6) DALLY, G. F.: The rôle of calcium in tuberculosis, British J. Tuberc., April, 1929, xxiii.

HETEROALLERGY IN TUBERCULOSIS

The Tissue Reaction of Tuberculous Animals to Pathogenic Microörganisms[1]

J. WEISSFEILER

In a preceding paper (6) it was stated that, contrary to the current belief, Koch's phenomenon does not depend on the immunity produced by infection in a tuberculous animal and that it is not a manifestation of the specific tuberculin allergy of such an animal. Intracutaneous injections of apathogenic microörganisms, such as actinomyces, diphtheroids and sarcines, into a tuberculous animal cause a reaction which is identical with the classical Koch phenomenon in its histological development. (See figures 1 and 2.) This reaction of tuberculous animals to nonspecific microörganisms occurs with the same regularity as that to tubercle bacilli. It is designated "heteroallergy." It may be expected that this reaction influences the course of nonspecific infections in tuberculous animals. It is therefore of importance to investigate how this heteroallergy modifies the course of nonspecific infections following a primary tuberculous infection.

During the last few years some observations pertinent to these questions have been made, but it was impossible to explain these findings on a scientific basis. Calmette stated that the death-rate in children vaccinated with *BCG* was greatly decreased and that this decrease was not only due to the reduction of tuberculosis, but to the reduction of other causes of disease as well. Similar observations, on careful and statistically reliable data, were made in the U.S.S.R. Calmette and his coworkers attempted to investigate this interesting fact by suitable experiments. Ninni and de Sanctis Monaldi (5) infected two series of guinea pigs with anthrax bacilli; one series had been treated before with *BCG*, while the other series was not so treated. Animals vaccinated with *BCG* showed a higher resistance towards anthrax infection than the controls. Similar findings were obtained with Bang bacilli; the mortality of the control animals was twice as high as that of the *BCG*-treated animals. Calmette and Saenz (2) found that *BCG*-treated guinea pigs were much more resistant to inhalation infection with virulent pneumococci than

[1] From the Central Institute for Tuberculosis, Moscow.

normal animals. These authors claim that this protection is produced by *BCG*, but not by virulent tubercle bacilli. These findings are not in

FIG. 1. Guinea pig no. 388. Reinfection with tubercle bacilli. Typical Koch's phenomenon 5 days after the reinfection.

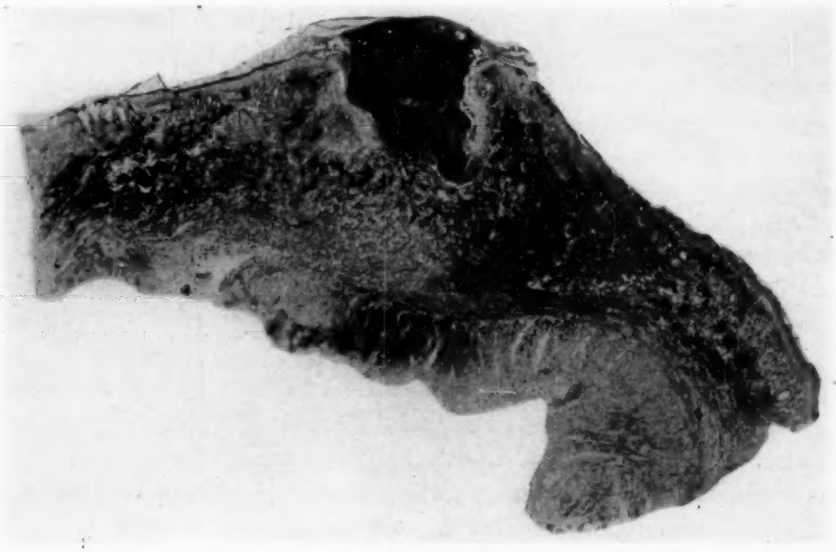


FIG. 2. Guinea pig no. 33. Reinfection with Actinomyces W. Typical Koch's phenomenon 3 days after the injection.

accord with previous work by Hyrayama, and Friedberger and Gurwitz. Hyrayama (4) observed an increased resistance of animals infected with virulent tubercle bacilli toward anthrax bacilli and virulent streptococci

as compared with normal guinea pigs. Friedberger and Gurwitz (3) found similar, although less definite, differences between tuberculous and normal guinea pigs in regard to their resistance against infection with *Cholera vibrio*. Bieling and Oelrichs (1) report that tuberculous rabbits reacted more vigorously to infection with *B. coli* and pneumococci, but that the outcome of the acute infection was often more favorable in the tuberculous than in the normal animals.

Hyrayama attempts to explain his findings by assuming that some sort of an antagonism exists between tubercle bacilli on the one hand, and anthrax bacilli and streptococci on the other. Calmette and his coworkers believe that *BCG*, but not virulent tubercle bacilli, produced what they termed "a paraspecific immunity."

EXPERIMENTAL DATA

Parallel series of tuberculous and normal guinea pigs and rabbits were infected intracutaneously with 0.1 cc. of a suspension of *Staphylococcus aureus*, this suspension corresponding in density to a suspension of *B. coli* containing 500,000,000 organisms per cubic centimetre. The intracutaneous route of infection was chosen in order to make possible macroscopical observation and to facilitate the comparison of histological changes in the local lesions with the changes in the classical Koch phenomenon. Sixteen rabbits and 14 guinea pigs were studied. The tuberculous animals reacted very differently to the infection with staphylococcus as compared with normal animals. In normal animals an abscess is formed which undergoes gradual resorption. In the tuberculous animal a light yellow pustule is formed surrounded by a narrow hyperaemic zone which appears within one or two days. This is followed by a recession of the inflammatory process and the formation of a scab which adheres until the cutaneous lesion is epithelialized.

Histologically, the difference between the reaction in the tuberculous and nontuberculous animal is very striking. In the latter there appears an abscess-formation in the subcutaneous connective tissue accompanied by a leucocytic infiltration. In the tuberculous animal this lesion is much more strictly localized and surrounds a central necrotic zone. The latter becomes separated and transformed into a scab under which regeneration of epithelium develops. Just like in Koch's phenomenon, the reaction is a quickly developing exudation, followed by necrosis and sequestration. (See figures 3 and 4.)

The final outcome of the infection is the same in the tuberculous and nontuberculous animals, but the healing of the local infection develops

somewhat faster in the tuberculous animal. Nontuberculous animals, which were previously infected by staphylococci and became immunized to staphylococci, reacted to the second injection. It seems therefore not justified to speak of an immunity reaction in tuberculous animals.

FIG. 3. Guinea pig no. 73, not tuberculous. Formation of abscess 3 days after the infection with staphylococci.

FIG. 4. Guinea pig no. 31, tuberculous. Central necrosis with sharply limited narrow infiltration, 3 days after infection with staphylococci.

The rapid inflammatory reaction, its sharp demarcation and the expulsion of the necrotic centre represent a reaction which is likely to diminish, or, at least, retard the spread of infection. This heteroallergic reaction in the skin of tuberculous animals has probably its equivalent in other organs, thus explaining the facts observed by Hyrayama, Friedberger and Gurwitz, and Calmette and his coworkers. These findings

would show that Calmette's statement concerning the peculiar faculty of *BCG*, as contrasted with virulent tubercle bacilli, to produce a nonspecific increase of resistance, is unwarranted. The experiments reported lead to conclusions similar to those of Bieling and Oelrichs.

The experiments which were reported above and which established the heteroallergic reactions in tuberculous animals should be extended to other acute infectious diseases. It seems possible that certain acute infections in animals may be greatly modified by preëxisting tuberculous infection, and may, under such conditions, produce a course which is more similar to that observed in human beings.

SUMMARY

1. Apathogenic microörganisms injected into tuberculous animals produce a reaction which differs from that in healthy animals. A similar difference is observed when *Staphylococcus aureus* is injected.

2. Intracutaneous injections of staphylococci into tuberculous animals causes a tissue reaction which is comparable to Koch's phenomenon, a rapid cellular exudation followed by necrosis.

3. This heteroallergic reaction may, in certain circumstances, modify the course of a nonspecific infection in a tuberculous animal. The difference of the course of an acute infection in a tuberculous animal as compared to a healthy animal is not due to an antagonism between the two infecting agents, but it is due to a nonspecific process.

4. The recognition of the significance of heteroallergy should encourage the study of the nonspecific factors in phthisiogenesis. These findings form an anatomical and biological basis for the apparent resistance of tuberculous animals to other infections.

REFERENCES

(1) Bieling and Oelrichs: Die Kochbazilleninfektion in Wechselwirkung zu andersartigen Infektionen, Ztschr. Tuberk., 1934, lix, 242.

(2) Calmette and Saenz: Sur l'immunité paraspécifique conferée par le *BCG*, Ann. Inst. Pasteur, 1933, l, 433.

(3) Friedberger and Gurwitz: Hat die hochgradige Infektion mit Tuberkelbazillen einen Einfluss auf den Ablauf der intraperitonealen Cholerainfektion gegenüber normalen Kontrollen, Ztschr. Immunitätsforsch. u. exper. Therap., 1931, lxxii, 180.

(4) Hyrayama: Über die Resistenz tuberkulös infizierter Tiere gegen andere nachträgliche Infektionen, Ibid., 1930, lxviii, 218.

(5) Ninni and de Sanctis Monaldi: Allure de l'infection à bacille de Bang et de l'intoxication diphthérique chez les cobayes traités par le *BCG*, Compt. Rend. Soc. Biol., 1932, cix, 1091.

(6) Weissfeiler: Untersuchungen über Heteroallergie bei Tuberkulose. I. Der unspezifische Mechanismus des Kochschen Phänomens, Ztschr. f. Immunitätsforsch. u. exper. Therap., 1934, lxxxiii.

A GLYCEROL-FREE MEDIUM FOR THE TUBERCLE BACILLUS[1]

R. R. HENLEY

Synthetic media, because of the simplicity of their composition, are now generally used for the cultivation of the tubercle bacillus when the chemistry of the organism and its products is studied. The source of nitrogen in such media is asparagin, either alone or with small amounts of ammonium salts, while glycerol is used as the source of carbon. Asparagin contains an amino and an amido group. The presence of the two groups complicates the study of the nitrogen metabolism of the microörganism, while glycerol is difficult to estimate accurately when in solution with other organic compounds.

During the course of studies of the biology of the tubercle bacillus in these laboratories, a medium has been devised which contains neither amino acids nor glycerol, but which nevertheless affords an abundant growth of the human type of the organism. Since a medium of this type may be of value to those engaged in the study of the metabolic processes of the tubercle bacillus the following notes are presented:

	gm.
Ammonium malate, $(NH_4)_2C_4H_4O_6$	12.53
Dipotassium phosphate, $K_2HPO_4 + 3\ H_2O$., C.P.	1.80
Sodium citrate, $Na_3C_6H_5O_7 + 5\frac{1}{2}\ H_2O$., C.P.	0.75
Magnesium sulphate, $MgSO_4 + 7\ H_2O$, U. S. P.	1.50
Ferric citrate, scales, U. S. P. VIII	.30
Dextrose, of the grade known as *Cerelose*	80.00
	cc.
Water, distilled, to make	1,000.00

Preparation of the Medium

The ammonium malate is prepared by dissolving 10 gm. of malic acid (grade known as "Food Pure") in about 500 cc. of distilled water. Ammonium hydroxide, C.P., is added to the solution until this is neutral to litmus. The other ingredients of the medium are then added in the amounts and order given in the formula. Each compound is dissolved

[1] From the Biochemic Division, Bureau of Animal Industry, U. S. Department of Agriculture, Washington, D. C.

completely before the next is added. The required amount of ferric citrate is dissolved in hot water before it is added to the solution.

The completed medium is placed in 300-cc. Erlenmeyer flasks, 100 cc. per flask, and is sterilized by heating under 10 to 12 lbs. steam pressure for 20 minutes, or, alternatively, by heating in flowing steam for 30, 20 and 15 minutes, respectively, on each of three successive days. Heating causes a lowering of the pH value; hence excessive heating must be avoided. The pH value of the sterilized medium should not be lower than 6.0. It is possible and desirable so to prepare and sterilize the medium that the pH will be not lower than 6.4 nor higher than 7.

Cultivation of the Tubercle Bacillus

The sterilized medium is inoculated with seed from vigorously growing cultures not more than 14 days old, and the inoculated medium is incubated at 37.5°C.

Growth starts slowly, requiring four weeks or longer to reach 0.50 gm. dry weight of bacilli per 100 cc. of culture medium, but, once started, it continues steadily and reaches a maximum about the eighth week. The greatest weight thus far obtained is 1.82 gm. per 100 cc. culture fluid, and the average weight of bacteria in mature cultures is approximately 1.60 gm. per 100 cc. As with other media, the weight of bacteria reaches a maximum and then tends to decrease. Growth is not always uniform, since differences in weight are frequently found between two or more cultures of the same age and batch.

Three strains of the human, three of the bovine, and six of the avian type of tubercle bacilli have been tried on the dextrose-malate medium. The three strains of the human type grew abundantly. Two strains of the bovine type grew, but not so well as the human, and the third bovine strain failed to grow. All of the 6 avian strains grew poorly, and in appearance the avian cultures were entirely unlike the human and bovine cultures. Whereas all of the human and two of the bovine strains formed dry, thick, slightly cream-colored and heavily wrinkled pellicles, the 6 avian strains formed moist, thin, grayish, smooth and somewhat slimy pellicles, which had a tendency to fall and then to form new growth across the surface.

In every experiment in which the reactions of cultures of the human type on the dextrose-malate medium have been followed, the cultures became more acid (as low as pH 5.4) in the earlier stages and more alkaline in the later stages of growth. The reaction curves of cultures

on this medium are therefore practically the reverse of reaction curves of cultures on glycerol-asparagin media, since on the latter media cultures become more alkaline in the earlier stages and tend to become acid in the later stages of growth. The reactions of cultures of the avian and bovine types on the dextrose-malate medium have not been followed.

Analyses of several lots of culture fluid at different periods of growth indicate that the amounts of total solids, reducing sugar and ammonia nitrogen may decrease by 90 per cent or more during the growth of the bacteria. Thus, in one experiment total solids decreased from 10.79 to 1.26 gm. per 100 cc. of medium, reducing sugar decreased from 8.18 to 0.11 gm. and ammonia nitrogen from 0.18 to 0.01 gm. during the ten weeks of incubation. Almost complete utilization of the dextrose and nitrogen is thus indicated.

Although 8 per cent of dextrose is provided in the formula given above, as much as 10 per cent has been used successfully. However, the increased amount of dextrose affords only a very slightly increased amount of growth and renders the medium more susceptible to injury during sterilization. No growth has been obtained on media which contained 12 per cent of dextrose. It may be added that arabinose, galactose, lactose, levulose, maltose, mannose and saccharose have also been tested as substitutes for glycerol. Of these only saccharose afforded appreciable growth and even then the thin growth barely covered the surface.

The abundant growth of the human type of tubercle bacillus on the dextrose-malate medium shows that the organism is able to thrive on culture media which contain neither amino acids nor glycerol.

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ABSTRACTS OF TUBERCULOSIS

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Tuberculosis Problem.—The two main problems of tuberculosis are early diagnosis and treatment and adequate after-care. The number of early cases admitted differs among various sanatoria, but the usual experience is from 17 to 25 per cent and rarely over 40 per cent in the most favorable circumstances. Of 2,760 patients treated between 1903 and 1919, 40 per cent were living 13 to 19 years after discharge. Of the early cases in this group, 64 per cent were alive at the end of 19 years. From a series of cases it was concluded that there was a delayed or mistaken diagnosis in 25 per cent. There was an unreasonable delay in consulting a doctor in 20 per cent when symptoms were present, and no unreasonable delay in 74 per cent when the onset was sudden or asymptomatic. Six per cent were discovered on routine examination. From a group of 100 cases from the more educated and wealthier classes, it was concluded that the doctor was unduly slow in making a diagnosis in 36 of them, and the patient delayed unduly consulting a doctor in 20. Although great advance has been made in the last 20 years in the early diagnosis of tuberculosis no very great decrease has occurred in the time between appearance of symptoms and the application of treatment. Twenty years ago this time averaged 18 months. The only feasible remedy is to educate the public as to symptoms and dangers of tuberculosis and to search for cases. The State provides quite adequate treatment for the notified patient, but does not guarantee the provision of permanent security with treatment nor adequately provide for maintenance of the family. There are two classes of patients to be considered: (1) the advanced incurable case and (2) the curable case. Some of the former leave the sanatorium and go home, while others are provided for in homes for the incurable sick or infectious-disease hospitals. The public-assistance institutions might also be made more suitable for the advanced case. For the curable case, adequate after-care is essential and is represented in its best form in the settlement where hospital, sanatorium and settlement are located at one centre. Accommodations in a settlement cannot yet be offered all patients and less complete measures are being tried.—*Our Difficulties in the Conflict against Tuberculosis, F. W. Burton-Fanning, J. State Med., September, 1934, xlii, 497.*—(*L. F. B.*)

Massachusetts Tuberculosis League.—In May, 1933, at the request of Mayor Russell of Cambridge, the League undertook to make a study of tuberculosis and facilities for handling it in that city. Through Dr. Kendall Emerson of the National Tuberculosis Association, the services of Dr. Carl E. Buck, Field Secretary, American Public